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#### (54) Title: 5' ESTS AND ENCODED HUMAN PROTEINS

#### (57) Abstract

The sequences of 5' ESTs derived from mRNAs encoding secreted proteins are disclosed. The 5' ESTs may be to obtain cDNAs and genomic DNAs corresponding to the 5' ESTs. The 5' ESTs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. Upstream regulatory sequences may also be otained using the 5' ESTs. The 5' ESTs may also be used to design expression vectors and secretion vectors.

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#### 5' ESTS AND ENCODED HUMAN PROTEINS

#### Background of the Invention

The estimated 50,000-100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced. Potential open reading frames in these genomic sequences are identified using bioinformatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bioinformatics software may mischaracterize the genomic sequences obtained, *i.e.*, labeling non-coding DNA as coding DNA and vice versa.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding portions of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify extended cDNAs which include sequences adjacent to the EST sequences. The extended cDNAs may contain all of the sequence of the EST which was used to obtain them or only a portion of the sequence of the EST which was used to obtain them. In addition, the extended cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the extended cDNAs may include portions of the coding sequence of the gene from which the EST was derived. It will be appreciated that there may be several extended cDNAs which include the EST sequence as a result of alternate splicing or the activity of alternative promoters. Alternatively, ESTs having partially overlapping sequences may be identified and contigs comprising the consensus sequences of the overlapping ESTs may be identified.

In the past, these short EST sequences were often obtained from oligo-dT primed cDNA

35 libraries. Accordingly, they mainly corresponded to the 3' untranslated region of the mRNA. In part,
the prevalence of EST sequences derived from the 3' end of the mRNA is a result of the fact that typical

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techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5' ends of mRNAs (Adams et al., Nature 377:3-174, 1996, Hillier et al., Genome Res. 6:807-828, 1996).

In addition, in those reported instances where longer cDNA sequences have been obtained, the reported sequences typically correspond to coding sequences and do not include the full 5' untranslated region (5'UTR) of the mRNA from which the cDNA is derived. Indeed, 5'UTRs have been shown to affect either the stability or translation of mRNAs. Thus, regulation of gene expression may be achieved through the use of alternative 5'UTRs as shown, for instance, for the translation of the tissue inhibitor of metalloprotease mRNA in mitogenically activated cells (Waterhouse et al., J Biol Chem. 265:5585-9, 1990). Furthermore, modification of 5'UTR through mutation, insertion or translocation events 10 may even be implied in pathogenesis. For instance, the fragile X syndrome, the most common cause of inherited mental retardation, is partly due to an insertion of multiple CGG trinucleotides in the 5'UTR of the fragile X mRNA resulting in the inhibition of protein synthesis via ribosome stalling (Feng et al, Science 268:731-4, 1995). An aberrant mutation in regions of the 5'UTR known to inhibit translation of the proto-oncogene c-myc was shown to result in upregulation of c-myc protein 15 levels in cells derived from patients with multiple myelomas (Willis et al, Curr Top Microbiol Immunol 224:269-76, 1997). In addition, the use of oligo-dT primed cDNA libraries does not allow the isolation of complete 5'UTRs since such incomplete sequences obtained by this process may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5' ends of mRNAs.

While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. In some instances, the sequences used in such therapeutic or diagnostic techniques may be sequences which encode proteins which are secreted from the cell in which they are synthesized. Those sequences encoding secreted proteins as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and may be responsible for producing a clinically relevant response in their target cells. In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon-α, interferon-β, interferon-γ, and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy-induced neutropenia and multiple sclerosis. For these reasons, extended cDNAs encoding secreted proteins or portions thereof represent a valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

In addition to being therapeutically useful themselves, secretory proteins include short peptides, called signal peptides, at their amino termini which direct their secretion. These signal peptides are

encoded by the signal sequences located at the 5' ends of the coding sequences of genes encoding secreted proteins. These signal peptides can be used to direct the extracellular secretion of any protein to which they are operably linked. In addition, portions of the signal peptides called membranetranslocating sequences, may also be used to direct the intracellular import of a peptide or protein of 5 interest. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cells in which it is produced. Signal sequences encoding signal peptides also find application in simplifying protein purification techniques. In such applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. Thus, there exists a need to identify 10 and characterize the 5' portions of the genes for secretory proteins which encode signal peptides.

Sequences coding for non-secreted proteins may also find application as therapeutics or diagnostics. In particular, such sequences may be used to determine whether an individual is likely to express a detectable phenotype, such as a disease, as a consequence of a mutation in the coding sequence of a protein. In instances where the individual is at risk of suffering from a disease or other undesirable 15 phenotype as a result of a mutation in such a coding sequence, the undesirable phenotype may be corrected by introducing a normal coding sequence using gene therapy. Alternatively, if the undesirable phenotype results from overexpression of the protein encoded by the coding sequence, expression of the protein may be reduced using antisense or triple helix based strategies.

The secreted or non-secreted human polypeptides encoded by the coding sequences may also be 20 used as therapeutics by administering them directly to an individual having a condition, such as a disease, resulting from a mutation in the sequence encoding the polypeptide. In such an instance, the condition can be cured or ameliorated by administering the polypeptide to the individual.

In addition, the secreted or non-secreted human polypeptides or portions thereof may be used to generate antibodies useful in determining the tissue type or species of origin of a biological sample. The 25 antibodies may also be used to determine the cellular localization of the secreted or non-secreted human polypeptides or the cellular localization of polypeptides which have been fused to the human polypeptides. In addition, the antibodies may also be used in immunoaffinity chromatography techniques to isolate, purify, or enrich the human polypeptide or a target polypeptide which has been fused to the human polypeptide.

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Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of 35 them consists of making a CpG island library (Cross et al., Nature Genetics 6: 236-244, 1994). The second consists of isolating human genomic DNA sequences containing SpeI binding sites by the use of Spel binding protein. (Mortlock et al., Genome Res. 6:327-335, 1996). Both of these approaches have

their limits due to a lack of specificity and of comprehensiveness. Thus, there exists a need to identify and systematically characterize the 5' portions of the genes.

The present 5' ESTs may be used to efficiently identify and isolate 5'UTRs and upstream regulatory regions which control the location, developmental stage, rate, and quantity of protein 5 synthesis, as well as the stability of the mRNA. Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, ESTs containing the 5' ends of protein genes may include sequences useful as probes for chromosome mapping and the identification of individuals. Thus, there is a need to identify 10 and characterize the sequences upstream of the 5' coding sequences of genes.

#### Summary of the Invention

The present invention relates to purified, isolated, or enriched 5' ESTs which include sequences derived from the authentic 5' ends of their corresponding mRNAs. The term "corresponding mRNA" 15 refers to the mRNA which was the template for the cDNA synthesis which produced the 5' EST. These sequences will be referred to hereinafter as "5' ESTs." The present invention also includes purified, isolated or enriched nucleic acids comprising contigs assembled by determining a consensus sequences from a plurality of ESTs containing overlapping sequences. These contigs will be referred to herein as "consensus contigated 5'ESTs."

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As used herein, the term "purified" does not require absolute purity; rather, it is intended as a relative definition. Individual 5' EST clones isolated from a cDNA library have been conventionally purified to electrophoretic homogeneity. The sequences obtained from these clones could not be obtained directly either from the library or from total human DNA. The cDNA clones are not naturally occurring as such, but rather are obtained via manipulation of a partially purified naturally occurring 25 substance (messenger RNA). The conversion of mRNA into a cDNA library involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection. Thus, creating a cDNA library from messenger RNA and subsequently isolating individual clones from that library results in an approximately 104-106 fold purification of the native message. Purification of starting material or natural material to at least one order of magnitude, 30 preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturallyoccurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, 35 separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the 5' EST is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the 5' ESTs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched 5' ESTs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched 5' ESTs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched 5' ESTs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules.

"Stringent," "moderate," and "low" hybridization conditions are as defined below.

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The term "polypeptide" refers to a polymer of amino acids without regard to the length of the polymer; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide. This term also does not specify or exclude post-expression modifications of polypeptides, for example, polypeptides which include the covalent attachment of glycosyl groups, acetyl groups, phosphate groups, lipid groups and the like are expressly encompassed by the term polypeptide. Also included within the definition are polypeptides which contain one or more analogs of an amino acid (including, for example, non-naturally occurring amino acids, amino acids which only occur naturally in an unrelated biological system, modified amino acids from mammalian systems etc.), polypeptides with substituted linkages, as well as other modifications known in the art, both naturally occurring and non-naturally occurring.

As used interchangeably herein, the terms "nucleic acids," "oligonucleotides," and "polynucleotides" include RNA, DNA, or RNA/DNA hybrid sequences of more than one nucleotide in either single chain or duplex form. The term "nucleotide" as used herein as an adjective to describe molecules comprising RNA, DNA, or RNA/DNA hybrid sequences of any length in single-stranded or duplex form. The term "nucleotide" is also used herein as a noun to refer to individual nucleotides or varieties of nucleotides, meaning a molecule, or individual unit in a larger nucleic acid molecule, comprising a purine or pyrimidine, a ribose or deoxyribose sugar moiety, and a phosphate group, or phosphodiester linkage in the case of nucleotides within an oligonucleotide or polynucleotide. Although the term "nucleotide" is also used herein to encompass "modified nucleotides" which comprise at least one modifications (a) an alternative linking group, (b) an analogous form of purine, (c) an analogous form of pyrimidine, or (d) an analogous sugar, for examples of analogous linking groups, purine, pyrimidines, and sugars see for example PCT publication No. WO 95/04064. The polynucleotide sequences of the invention may be prepared by any known method, including synthetic, recombinant, ex vivo generation, or a combination thereof, as well as utilizing any purification methods known in the art.

The terms "base paired" and "Watson & Crick base paired" are used interchangeably herein to refer to nucleotides which can be hydrogen bonded to one another be virtue of their sequence

identities in a manner like that found in double-helical DNA with thymine or uracil residues linked to adenine residues by two hydrogen bonds and cytosine and guanine residues linked by three hydrogen bonds (See Stryer, L., Biochemistry, 4th edition, 1995).

The terms "complementary" or "complement thereof" are used herein to refer to the 5 sequences of polynucleotides which are capable of forming Watson & Crick base pairing with another specified polynucleotide throughout the entirety of the complementary region. For the purpose of the present invention, a first polynucleotide is deemed to be complementary to a second polynucleotide when each base in the first polynucleotide is paired with its complementary base. Complementary bases are, generally, A and T (or A and U), or C and G. "Complement" is used 10 herein as a synonym from "complementary polynucleotide," "complementary nucleic acid" and "complementary nucleotide sequence". These terms are applied to pairs of polynucleotides based solely upon their sequences and not any particular set of conditions under which the two polynucleotides would actually bind. Preferably, a "complementary" sequence is a sequence which an A at each position where there is a T on the opposite strand, a T at each position where there is an A on 15 the opposite strand, a G at each position where there is a C on the opposite strand and a C at each position where there is a G on the opposite strand.

Thus, 5' ESTs in cDNA libraries in which one or more 5' ESTs make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant 5' ESTs" as defined herein. Likewise, 5' ESTs in a population of plasmids in which one or more 5' ESTs of the present 20 invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are "enriched recombinant 5' ESTs" as defined herein. However, 5' ESTs in cDNA libraries in which 5' ESTs constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in which backbone molecules having a 5' EST insert are extremely rare, are not "enriched recombinant 5' ESTs."

In some embodiments, the present invention relates to 5' ESTs which are derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble proteins), or partially (e.g. receptors) from the cell in which they are expressed. 30 "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

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Such 5' ESTs include nucleic acid sequences, called signal sequences, which encode signal peptides which direct the extracellular secretion of the proteins encoded by the genes from which the 5' ESTs are derived. Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation WO 99/53051 PCT/IB99/00712

of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across 5 the cell membrane.

The 5' ESTs of the present invention have several important applications. For example, they may be used to obtain and express cDNA clones which include the full protein coding sequences of the corresponding gene products, including the authentic translation start sites derived from the 5' ends of the coding sequences of the mRNAs from which the 5' ESTs are derived. These cDNAs will be referred 10 to hereinafter as "full-length cDNAs." These cDNAs may also include DNA derived from mRNA sequences upstream of the translation start site. The full-length cDNA sequences may be used to express the proteins corresponding to the 5' ESTs. As discussed above, secreted proteins and non-secreted proteins may be therapeutically important. Thus, the proteins expressed from the cDNAs may be useful in treating and controlling a variety of human conditions. The 5' ESTs may also be used to obtain the 15 corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes the mRNA from which the 5' EST was derived.

Alternatively, the 5' ESTs may be used to obtain and express extended cDNAs encoding portions of the protein. In the case of secreted proteins, the portions may comprise the signal peptides of the secreted proteins or the mature proteins generated when the signal peptide is cleaved off.

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The present invention includes isolated, purified, or enriched "EST-related nucleic acids." The terms "isolated," "purified" or "enriched" have the meanings provided above. As used herein, the term "EST-related nucleic acids" means the nucleic acids of SEQ ID NOs. 24-811 and 1600-1622, extended cDNAs obtainable using the nucleic acids of SEQ ID NOs. 24-811 and 1600-1622, full-length cDNAs obtainable using the nucleic acids of SEQ ID NOs. 24-811 and 1600-1622 or genomic DNAs obtainable 25 using the nucleic acids of SEQ ID NOs. 24-811 and 1600-1622. The present invention also includes the sequences complementary to the EST-related nucleic acids.

The present invention also includes isolated, purified, or enriched "fragments of EST-related nucleic acids." The terms "isolated," "purified" and "enriched" have the meanings described above. As used herein the term "fragments of EST-related nucleic acids" means fragments comprising at least 10, 30 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, 50, 75, 100, 200, 300, 500, or 1000 consecutive nucleotides of the EST-related nucleic acids to the extent that fragments of these lengths are consistent with the lengths of the particular EST-related nucleic acids being referenced. In particular, fragments of EST-related nucleic acids refer to "polynucleotides described in Table II," "polynucleotides described in Table III," and "polynucleotides described in Table IV." The present invention also includes the sequences 35 complementary to the fragments of the EST-related nucleic acids.

The present invention also includes isolated, purified, or enriched "positional segments of ESTrelated nucleic acids." As used herein, the term "positional segments of EST-related nucleic acids"

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includes segments comprising nucleotides 1-25, 26-50, 51-75, 76-100, 101-125, 126-150, 151-175, 176-200, 201-225, 226-250, 251-300, 301-325, 326-350, 351-375, 376-400, 401-425, 426-450, 451-475, 476-500, 501-525, 526-550, 551-575, 576-600 and 601-the terminal nucleotide of the EST-related nucleic acids to the extent that such nucleotide positions are consistent with the lengths of the particular 5 EST-related nucleic acids being referenced. The term "positional segments of EST-related nucleic acids also includes segments comprising nucleotides 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 450-500, 501-550, 551-600 or 601-the terminal nucleotide of the EST-related nucleic acids to the extent that such nucleotide positions are consistent with the lengths of the particular EST-related nucleic acids being referenced. The term "positional segments of EST-related nucleic 10 acids" also includes segments comprising nucleotides 1-100, 101-200, 201-300, 301-400, 501-500, 500-600, or 601-the terminal nucleotide of the EST-related nucleic acids to the extent that such nucleotide positions are consistent with the lengths of the particular EST-related nucleic acids being referenced. In addition, the term "positional segments of EST-related nucleic acids" includes segments comprising nucleotides 1-200, 201-400, 400-600, or 601-the terminal nucleotide of the EST-related nucleic acids to 15 the extent that such nucleotide positions are consistent with the lengths of the particular EST-related nucleic acids being referenced. The present invention also includes the sequences complementary to the positional segments of EST-related nucleic acids.

The present invention also includes isolated, purified, or enriched "fragments of positional segments of EST-related nucleic acids." As used herein, the term "fragments of positional segments of EST-related nucleic acids" refers to fragments comprising at least 10, 15, 18, 20, 23, 25, 28, 30, 35, 40, 50, 75, 100, 150, or 200 consecutive nucleotides of the positional segments of EST-related nucleic acids. The present invention also includes the sequences complementary to the fragments of positional segments of EST-related nucleic acids.

The present invention also includes isolated or purified "EST-related polypeptides." As used

25 herein, the term "EST-related polypeptides" means the polypeptides encoded by the EST-related nucleic acids, including the polypeptides of SEQ ID NOs. 812-1599.

The present invention also includes isolated or purified "fragments of EST-related polypeptides." As used herein, the term "fragments of EST-related polypeptides" means fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of an EST-related polypeptide to the extent that fragments of these lengths are consistent with the lengths of the particular EST-related polypeptides being referenced. In particular, fragments of EST-related polypepides refer to polypeptides encoded by "polynucleotides described in Table II," "polynucleotides described in Table III," and "polynucleotides described in Table IV."

The present invention also includes isolated or purified "positional segments of EST-related polypeptides." As used herein, the term "positional segments of EST-related polypeptides" includes polypeptides comprising amino acid residues 1-25, 26-50, 51-75, 76-100, 101-125, 126-150, 151-175, 176-200, or 201-the C-terminal amino acid of the EST-related polypeptides to the extent that such amino

acid residues are consistent with the lengths of the particular EST-related polypeptides being referenced. The term "positional segments of EST-related polypeptides also includes segments comprising amino acid residues 1-50, 51-100, 101-150, 151-200 or 201-the C-terminal amino acid of the EST-related polypeptides to the extent that such amino acid residues are consistent with the lengths of the particular 5 EST-related polypeptides being referenced. The term "positional segments of EST-related polypeptides" also includes segments comprising amino acids 1-100 or 101-200 of the EST-related polypeptides to the extent that such amino acid residues are consistent with the lengths of particular EST-related polypeptides being referenced. In addition, the term "positional segments of EST-related polypeptides" includes segments comprising amino acid residues 1-200 or 201-the C-terminal amino acid of the EST-10 related polypeptides to the extent that amino acid residues are consistent with the lengths of the particular EST-related polypeptides being referenced.

The present invention also includes isolated or purified "fragments of positional segments of EST-related polypeptides." As used herein, the term "fragments of positional segments of EST-related polypeptides" means fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150. 15 consecutive amino acids of positional segments of EST-related polypeptides to the extent that fragments of these lengths are consistent with the lengths of the particular EST-related polypeptides being referenced.

The present invention also includes antibodies which specifically recognize the EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides. 20 or fragments of positional segments of EST-related polypeptides. In the case of secreted proteins, such as those of SEQ ID NOs. 1554-1580 antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the signal peptides of SEQ ID NOs. 812-1516 or 1554-1580 may also be obtained.

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In some embodiments and in the case of secreted proteins, the EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids, or fragments of positional segments of nucleic acids include a signal sequence. In other embodiments, the ESTrelated nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids, or fragments of positional segments of nucleic acids may include the full coding sequence for the 30 protein or, in the case of secreted proteins, the full coding sequence of the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids, or fragments of positional segments of nucleic acids may include regulatory regions upstream of the translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene 35 expression.

As discussed above, both secreted and non-secreted human proteins may be therapeutically important. Thus, the proteins expressed from the EST-related nucleic acids, fragments of EST-related WO 99/53051 PCT/IB99/00712

nucleic acids, positional segments of EST-related nucleic acids, or fragments of positional segments of nucleic acids may be useful in treating or controlling a variety of human conditions.

The EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids, or fragments of positional segments of nucleic acids may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from abnormal gene expression. In addition, the EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids, or fragments of positional segments of nucleic acids are useful for constructing a high resolution map of the human chromosomes.

The present invention also relates to secretion vectors capable of directing the secretion of a protein of interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired proteins.

The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids, or fragments of positional segments of nucleic acids, such as promoters or upstream regulatory sequences.

The present invention also comprises fusion vectors for making chimeric polypeptides comprising a first polypeptide and a second polypeptide. Such vectors are useful for determining the cellular localization of the chimeric polypeptides or for isolating, purifying or enriching the chimeric polypeptides.

The EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids, or fragments of positional segments of nucleic acids may also be used for gene therapy to control or treat genetic diseases. In the case of secreted proteins, signal peptides may be fused to heterologous proteins to direct their extracellular secretion.

Bacterial clones containing Bluescript plasmids having inserts containing the sequence of the non-aligned 5'ESTs, also referred to as singletons, and sequences of the 5'ESTs which were aligned to yield consensus contigated 5' ESTs are presently stored at 80°C in 4% (v/v) glycerol in the inventor's laboratories under internal designations. The non-aligned 5'ESTs are those which comprise a single EST from a single tissue in the listing of Table V. The inserts may be recovered from the stored materials by growing the appropriate clones on a suitable medium. The Bluescript DNA can then be isolated using plasmid isolation procedures familiar to those skilled in the art such as alkaline lysis minipreps or large scale alkaline lysis plasmid isolation procedures. If desired the plasmid DNA may be further enriched by centrifugation on a cesium chloride gradient, size exclusion chromatography, or anion exchange chromatography. The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR

can be performed with primers designed at both ends of the inserted EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids, or fragments of positional segments of nucleic acids. The PCR product which corresponds to the EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids, or fragments of positional segments of nucleic acids can then be manipulated using standard cloning techniques familiar to those skilled in the art.

One embodiment of the present invention is a purified nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and sequences complementary to the sequences of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622.

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Another embodiment of the present invention is a purified nucleic acid comprising at least 10, 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, 50, 75, 100, 200, 300, 500, or 1000 consecutive nucleotides, to the extent that fragments of these lengths are consistent with the specific sequence, of a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and sequences complementary to the sequences of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622.

A further embodiment of the present invention is a purified nucleic acid comprising the coding sequence of a sequence selected from the group consisting of SEQ ID NOs. 24-811.

Yet another embodiment of the present invention is a purified nucleic acid comprising the full coding sequences of a sequence selected from the group consisting of SEQ ID NOs. 766-792 wherein the full coding sequence comprises the sequence encoding the signal peptide and the sequence encoding the mature protein.

Still another embodiment of the present invention is a purified nucleic acid comprising a contiguous span of a sequence selected from the group consisting of SEQ ID NOs. 766-792 which encodes the mature protein.

Another embodiment of the present invention is a purified nucleic acid comprising a

25 contiguous span of a sequence selected from the group consisting of SEQ ID NOs. 24-728 and 766792 which encodes the signal peptide.

Another embodiment of the present invention is a purified nucleic acid encoding a polypeptide comprising a sequence selected from the group consisting of the sequences of SEQ ID NOs. 812-1599.

Another embodiment of the present invention is a purified nucleic acid encoding a polypeptide comprising a sequence selected from the group consisting of the sequences of SEQ ID NOs. 1554-1580.

Another embodiment of the present invention is a purified nucleic acid encoding a polypeptide comprising a mature protein included in a sequence selected from the group consisting of the sequences of SEQ ID NOs. 1554-1580.

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Another embodiment of the present invention is a purified nucleic acid encoding a polypeptide comprising a signal peptide included in a sequence selected from the group consisting of the sequences of SEQ ID NOs. 812-1516 and 1554-1580.

Another embodiment of the present invention is a purified nucleic acid at least 30, 35, 40, 50. 75, 100, 200, 300, 500 or 1000 nucleotides in length which hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and sequences complementary to the sequences of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622.

Another embodiment of the present invention is a purified or isolated polypeptide comprising 10 a sequence selected from the group consisting of the sequences of SEQ ID NOs. 812-1599.

Another embodiment of the present invention is a purified or isolated polypeptide comprising a sequence selected from the group consisting of SEQ ID NOs. 1554-1580.

Another embodiment of the present invention is a purified or isolated polypeptide comprising a mature protein of a polypeptide selected from the group consisting of SEQ ID NOs. 1554-1580.

Another embodiment of the present invention is a purified or isolated polypeptide comprising a signal peptide of a sequence selected from the group consisting of the polypeptides of SEO ID NOs. 812-1516 and 1554-1580.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, 50, 75, 100, 200, 300, 500, or 1000 consecutive amino 20 acids, to the extent that fragments of these lengths are consistent with the specific sequence, of a sequence selected from the group consisting of the sequences of SEQ ID NOs. 812-1599.

Another embodiment of the present invention is a method of making a cDNA comprising the steps of contacting a collection of mRNA molecules from human cells with a primer comprising at least 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, or 50 consecutive nucleotides of a sequence selected from 25 the group consisting of the sequences complementary to SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, hybridizing said primer to an mRNA in said collection that encodes said protein reverse transcribing said hybridized primer to make a first cDNA strand from said mRNA, making a second cDNA strand complementary to said first cDNA strand and isolating the resulting cDNA encoding said protein comprising said first cDNA strand and said second cDNA strand.

Another embodiment of the present invention is a purified cDNA obtainable by the method of the preceding paragraph.

In one aspect of this embodiment, the cDNA encodes at least a portion of a human polypeptide.

Another embodiment of the present invention is a method of making a cDNA comprising the 35 steps of obtaining a cDNA comprising a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, contacting said cDNA with a detectable probe comprising at least 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, or 50 consecutive nucleotides of a sequence

selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and the sequences complementary to SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 under conditions which permit said probe to hybridize to said cDNA, identifying a cDNA which hybridizes to said detectable probe, and isolating said cDNA which hybridizes to said probe.

Another embodiment of the present invention is a purified cDNA obtainable by the method of the preceding paragraph.

In one aspect of this embodiment, the cDNA encodes at least a portion of a human polypeptide.

Another embodiment of the present invention is a method of making a cDNA comprising the steps of contacting a collection of mRNA molecules from human cells with a first primer capable of hybridizing to the polyA tail of said mRNA, hybridizing said first primer to said polyA tail, reverse transcribing said mRNA to make a first cDNA strand, making a second cDNA strand complementary to said first cDNA strand using at least one primer comprising at least 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, or 50 consecutive nucleotides of a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, and isolating the resulting cDNA comprising said first cDNA strand and said second cDNA strand.

Another embodiment of the present invention is a purified cDNA obtainable by the method of the preceding paragraph.

In one aspect of this embodiment, said cDNA encodes at least a portion of a human 20 polypeptide.

In another aspect of the preceding method the second cDNA strand is made by contacting said first cDNA strand with a first pair of primers, said first pair of primers comprising a second primer comprising at least 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, or 50 consecutive nucleotides of a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and a third primer having a sequence therein which is included within the sequence of said first primer, performing a first polymerase chain reaction with said first pair of primers to generate a first PCR product, contacting said first PCR product with a second pair of primers, said second pair of primers comprising a fourth primer, said fourth primer comprising at least 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, or 50 consecutive nucleotides of said sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, and a fifth primer, wherein said fourth and fifth hybridize to sequences within said first PCR product, and performing a second polymerase chain reaction, thereby generating a second PCR product.

One aspect of this embodiment is a purified cDNA obtainable by the method of the preceding paragraph.

In another aspect of this embodiment, said cDNA encodes at least a portion of a human polypeptide.

Alternatively, the second cDNA strand may be made by contacting said first cDNA strand with a second primer comprising at least 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, or 50 consecutive nucleotides of a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, hybridizing said second primer to said first strand cDNA, and extending said hybridized second primer to generate said second cDNA strand.

One aspect of the above embodiment is a purified cDNA obtainable by the method of the preceding paragraph.

In a further aspect of this embodiment said cDNA encodes at least a portion of a human polypeptide.

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sites.

Another embodiment of the present invention is a method of making a polypeptide comprising the steps of obtaining a cDNA which encodes a polypeptide encoded by a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 24-811 or a cDNA which encodes a polypeptide comprising at least 6, 8, 10, 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, or 50 consecutive amino acids of a polypeptide encoded by a sequence selected from the group consisting 15 of SEO ID NOs. 24-811, inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter, introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said cDNA, and isolating said protein.

Another aspect of this embodiment is an isolated protein obtainable by the method of the preceding paragraph.

20 Another embodiment of the present invention is a method of obtaining a promoter DNA comprising the steps of obtaining genomic DNA located upstream of a nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and the sequences complementary to the sequences of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, screening said genomic DNA to identify a promoter capable of directing transcription 25 initiation, and isolating said DNA comprising said identified promoter.

In one aspect of this embodiment, said obtaining step comprises walking from genomic DNA comprising a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and the sequences complementary to SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622. In another aspect of this embodiment, said screening step comprises inserting genomic DNA located 30 upstream of a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and the sequences complementary to SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 into a promoter reporter vector. For example, said screening step may comprise identifying motifs in genomic DNA located upstream of a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and the sequences complementary to SEO ID NOs. 35 24-811 and SEQ ID NOs. 1600-1622 which are transcription factor binding sites or transcription start Another embodiment of the present invention is a isolated promoter obtainable by the method of the paragraph above.

Another embodiment of the present invention is the inclusion of at least one sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, the sequences complementary to the sequences of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and fragments comprising at least 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, 50, or 100 consecutive nucleotides of said sequence in an array of discrete ESTs or fragments thereof of at least 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, 50, or 100 nucleotides in length. In some aspects of this embodiment, the array includes at least two sequences selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, the sequences complementary to the sequences of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, and fragments comprising at least 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, 50, or 100 consecutive nucleotides of said sequences. In another aspect of this embodiment, the array includes at least one, three, five, ten, fifteen, or twenty sequences selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, the sequences complementary to the sequences of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and fragments comprising at least 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, 50, or 100 consecutive nucleotides of said sequences.

Another embodiment of the present invention is an enriched population of recombinant nucleic acids, said recombinant nucleic acids comprising an insert nucleic acid and a backbone nucleic acid, wherein at least 0.01%, 0.05%, 0.1%, 0.5%, 1%, 2%, 5%, 10%, or 20% of said insert nucleic acids in said population comprise a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and the sequences complementary to SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a polypeptide comprising a sequence selected from the group consisting of SEO ID NOs. 812-1599.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a polypeptide comprising at least 6, 8, 10, 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, or 50 consecutive amino acids of a sequence selected from the group consisting of SEQ ID NOs. 812-1599.

Yet, another embodiment of the present invention is an antibody composition capable of selectively binding to an epitope-containing fragment of a polypeptide comprising a contiguous span of at least 8, 10, 12, 15, 18, 20, 23, 25, 28, 30, 35, 40, or 50 amino acids of any of SEQ ID NOs. 812-1599, wherein said antibody is polyclonal or monoclonal.

Another embodiment of the present invention is a computer readable medium having stored
thereon a sequence selected from the group consisting of a nucleic acid code of SEQ ID NOs. 24-811 and 1600-1622 and a polypeptide code of SEQ ID NOs. 812-1599.

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Another embodiment of the present invention is a computer system comprising a processor and a data storage device wherein said data storage device has stored thereon a sequence selected from the group consisting of a nucleic acid code of SEQID NOs. 24-811 and 1600-1622 and a polypeptide code of SEQ ID NOs. 812-1599. In one aspect of this embodiment the computer system further comprises a sequence comparer and a data storage device having reference sequences stored thereon. For example, the sequence comparer may comprise a computer program which indicates polymorphisms. In another aspect of this embodiment, the computer system further comprises an identifier which identifies features in said sequence.

Another embodiment of the present invention is a method for comparing a first sequence to a reference sequence wherein said first sequence is selected from the group consisting of a nucleic acid code of SEQID NOs. 24-811 and 1600-1622 and a polypeptide code of SEQ ID NOs. 812-1599 comprising the steps of reading said first sequence and said reference sequence through use of a computer program which compares sequences and determining differences between said first sequence and said reference sequence with said computer program. In some aspects of this embodiment, said step of determining differences between the first sequence and the reference sequence comprises identifying polymorphisms.

Another embodiment of the present invention is a method for identifying a feature in a sequence selected from the group consisting of a nucleic acid code of SEQID NOs. 24-811 and 1600-1622 and a polypeptide code of SEQ ID NOs. 812-1599 comprising the steps of reading said sequence through the use of a computer program which identifies features in sequences and identifying features in said sequence with said computer program.

Another embodiment of the present invention is a vector comprising a nucleic acid according to any one of the nucleic acids described above.

Another embodiment of the present invention is a host cell containing the above vector.

Another embodiment of the present invention is a method of making any of the nucleic acids described above comprising the steps of introducing said nucleic acid into a host cell such that said nucleic acid is present in multiple copies in each host cell and isolating said nucleic acid from said host cell.

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Another embodiment of the present invention is a method of making a nucleic acid of any of the nucleic acids described above comprising the step of sequentially linking together the nucleotides in said nucleic acids.

Another embodiment of the present invention is a method of making any of the polypeptides described above wherein said polypeptides is 150 amino acids in length or less comprising the step of sequentially linking together the amino acids in said polypeptide.

Another embodiment of the present invention is a method of making any of the polypeptides described above wherein said polypeptides is 120 amino acids in length or less comprising the step of sequentially linking together the amino acids in said polypeptides.

#### Brief Description of the Drawings

Figure 1 is a summary of a procedure for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they derived. In the first step (1), the cap of intact mRNAs is oxidized to be chemically ligated to an oligonucleotide tag. In the second step (2), a reverse transcription is performed using random primers to generate a first cDNA strand. In the third step (3), mRNAs are eliminated and the second strand synthesis is carried out using a primer contained in the oligonucleotide tag.

Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

Figure 3 summarizes a general method used to clone and sequence extended cDNAs containing sequences adjacent to 5'ESTs.

Figure 4 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags.

Figure 5 describes the transcription factor binding sites present in each of the promoters of Figure 4.

Figure 6 is a block diagram of an exemplary computer system.

Figure 7 is a flow diagram illustrating one embodiment of a process 200 for comparing a new nucleotide or protein sequence with a database of sequences in order to determine the homology levels between the new sequence and the sequences in the database.

Figure 8 is a flow diagram illustrating one embodiment of a process 250 in a computer for determining whether two sequences are homologous.

Figure 9 is a flow diagram illustrating one embodiment of an identifier process 300 for detecting the presence of a feature in a sequence.

Figure 10 is a table with all of the parameters that can be used for each step of extended cDNA analysis.

## Detailed Description of the Preferred Embodiment

30 I. Obtaining 5'ESTs from cDNA libraries including the 5'Ends of their Corresponding mRNAs

The 5' ESTs of the present invention were obtained from cDNA libraries including cDNAs which include the 5'end of their corresponding mRNAs. The general method used to obtain such cDNA libraries is described in Examples 1 to 5.

#### **EXAMPLE 1**

Preparation of mRNA

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Total human RNAs or polyA\* RNAs derived from 29 different tissues were respectively purchased from LABIMO and CLONTECH and used to generate 44 cDNA libraries as described below.

The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczyniski and Sacchi, *Analytical Biochemistry* 162:156-159, 1987). PolyA<sup>+</sup> RNA was isolated from total RNA (LABIMO) by two passes of oligo dT chromatography, as described by Aviv and Leder, *Proc. Natl. Acad. Sci. USA* 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the polyA+ RNAs were checked. Northern blots hybridized with a globin probe were used to confirm that the mRNAs were not degraded. Contamination of the polyA+ mRNAs by ribosomal sequences was checked using Northern blots and a probe derived from the sequence of the 28S rRNA. Preparations of mRNAs with less than 5% of rRNAs were used in library construction. To avoid constructing libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed fungal mRNAs was examined using PCR.

#### **EXAMPLE 2**

### Methods for Obtaining mRNAs having Intact 5' Ends

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Following preparation of the mRNAs from various tissues as described above, selection of mRNA with intact 5' ends and specific attachment of an oligonucleotide tag to the 5' end of such mRNA was performed using either a chemical or enzymatic approach. Both techniques takes advantage of the presence of the "cap" structure, which characterizes the 5'end of intact mRNAs and which comprises a guanosine generally methylated once, at the 7 position. The chemical approach is illustrated in Figure 1.

The chemical modification approach involves the optional elimination of the 2', 3'-cis diol of the 3' terminal ribose, the oxidation of the 2', 3', -cis diol of the ribose linked to the cap of the 5' ends of the mRNAs into a dialdehyde, and the coupling of the such obtained dialdehyde to a derivatized oligonucleotide tag. Further detail regarding the chemical approaches for obtaining mRNAs having intact 5' ends are disclosed in International Application No. WO96/34981, published November 7, 1996.

The enzymatic approach for ligating the oligonucleotide tag to the 5' ends of mRNAs with intact 5' ends involves the removal of the phosphate groups present on the 5' ends of uncapped incomplete mRNAs, the subsequent decapping of mRNAs with intact 5' ends and the ligation of the phosphate present at the 5' end of the decapped mRNA to an oligonucleotide tag. Further detail regarding the enzymatic approaches for obtaining mRNAs having intact 5' ends are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EP0 625572 and Kato et al., Gene 150:243-250 (1994).

In either the chemical or the enzymatic approach, the oligonucleotide tag has a restriction

35 enzyme site (e.g. EcoRI sites) therein to facilitate later cloning procedures. Following attachment of the oligonucleotide tag to the mRNA, the integrity of the mRNA was then examined by performing a Northern blot using a probe complementary to the oligonucleotide tag.

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#### **EXAMPLE 3**

#### cDNA Synthesis Using mRNA Templates Having Intact 5' Ends

For the mRNAs joined to oligonucleotide tags, first strand cDNA synthesis was performed using a reverse transcriptase with random nonamers as primers. In order to protect internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of mRNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

The second strand of the cDNA was synthesized with a Klenow fragment using a primer corresponding to the 5'end of the ligated oligonucleotide. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

#### **EXAMPLE 4**

Cloning of cDNAs derived from mRNA with intact 5' ends into BlueScript

Following second strand synthesis, the ends of the cDNA were blunted with T4 DNA polymerase (Biolabs) and the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only hemi-methylated site, hence the only site susceptible to EcoRI digestion. The cDNA was then size fractionated using exclusion chromatography (AcA, Biosepra) and fractions corresponding to cDNAs of more than 150 bp were pooled and ethanol precipitated. The cDNA was directionally cloned into the SmaI and EcoRI ends of the phagemid pBlueScript vector (Stratagene). The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

25 EXAMPLE 5

#### Selection of Clones Having the Oligonucleotide Tag Attached Thereto

Clones containing the oligonucleotide tag attached were then selected as follows. The plasmid DNAs containing 5' EST libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang et al., Gene 127:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The resulting single stranded DNA was then purified using paramagnetic beads as described by Fry et al., Biotechniques, 13: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3' end of the oligonucleotide tag.

Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double

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stranded DNA using a DNA polymerase such as the Thermosequenase obtained from Amersham Pharmacia Biotech. The double stranded DNA was then electroporated into bacteria. The percentage of positive clones having the 5' tag oligonucleotide was estimated using dot blot analysis to typically be between 90 and 98%.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP and sequenced as described below.

#### **EXAMPLE 6**

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Amersham.

#### Sequencing of Inserts in Selected Clones

Plasmid inserts were first amplified by PCR on PE-9600 thermocyclers (Perkin-Elmer, Applied Biosystems Division, Foster City, CA), using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer).

Sequencing reactions were performed using PE 9600 thermocyclers with standard dye-primer chemistry and ThermoSequenase (Amersham Pharmacia Biotech). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from

Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by

Following the sequencing reaction, the samples were precipitated with ethanol, resuspended in formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing Analysis Software, version 2.1.2.

#### **EXAMPLE 7**

# Obtaining 5' ESTs from Extended cDNA libraries Obtained from mRNA with Intact 5' Ends

Alternatively, 5'ESTs may be isolated from other cDNA or genomic DNA libraries. Such cDNA or genomic DNA libraries may be obtained from a commercial source or made using other techniques familiar to those skilled in the art. One example of such cDNA library construction, a full-length cDNA library, is as follows.

PolyA+ RNAs are prepared and their quality checked as described in Example 1. Then, the

caps at the 5' ends of the polyA+ RNAs are specifically joined to an oligonucleotide tag as described in

Example 2. The oligonucleotide tag may contain a restriction site such as Eco RI to facilitate further

subcloning procedures. Northern blotting is then performed to check the size of mRNAs having the oligonucleotide tag attached thereto and to ensure that the mRNAs are actually tagged.

First strand synthesis is subsequently carried out for mRNAs joined to the oligonucleotide tag as described in Example 3 above except that the random nonamers are replaced by an oligo-dT primer. For instance, this oligo-dT primer may contain an internal tag of 4 nucleotides which is different from one tissue to the other. Following second strand synthesis using a primer contained in the oligonucleotide tag attached to the 5' end of mRNA, the blunt ends of the obtained double stranded full-length DNAs are modified into cohesive ends to facilitate subcloning. For example, the extremities of full-length cDNAs may be modified to allow subcloning into the Eco RI and Hind III sites of a Bluescript vector using the Eco RI site of the oligonucleotide tag and the addition of a Hind III adaptor to the 3' end of full-length cDNAs.

The full-length cDNAs are then separated into several fractions according to their sizes using techniques familiar to those skilled in the art. For example, electrophoretic separation may be applied in order to yield 3 or 6 different fractions. Following gel extraction and purification, the cDNA fractions are subcloned into appropriate vectors, such as Bluescript vectors, transformed into competent bacteria and propagated under appropriate antibiotic conditions. Subsequently, plasmids containing tagged full-length cDNAs are positively selected as described in Example 5.

The 5' end of full-length cDNAs isolated from such cDNA libraries may then be sequenced as described in Example 6 to yield 5'ESTs.

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#### II. Computer Analysis of the Isolated 5' ESTs: Construction of the SignalTag™ Database

The sequence data from the cDNA libraries made as described above were transferred to a database, where quality control and validation steps were performed. A base-caller, working using a Unix system, automatically flagged suspect peaks, taking into account the shape of the peaks, the interpeak resolution, and the noise level. The base-caller also performed an automatic trimming. Any stretch of 25 or fewer bases having more than 4 suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the EST sequences. However, the resulting EST sequences may contain 1 to 5 bases belonging to the above mentioned sequences at their 5' end. If needed, these can easily be removed on a case to case basis.

Following sequencing as described above, the sequences of the 5' ESTs were entered in a database for storage and manipulation as described below. Before searching the ESTs in the database for sequences of interest, ESTs derived from mRNAs which were not of interest were identified. Briefly, such undesired sequences may be of three types. First, contaminants of either endogenous (ribosomal RNAs, transfert RNAs, mitochondrial RNAs) or exogenous (prokaryotic RNAs and fungal RNAs) origins were identified. Second, uninformative sequences, namely redundant sequences, small sequences and highly degenerate sequences were identified. Third, repeated sequences (Alu, L1, THE

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and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats) were identified and masked in further processing.

In order to determine the accuracy of the sequencing procedure as well as the efficiency of the 5' selection described above, the analyses described in Examples 8 and 9 respectively were performed 5 on 5'ESTs obtained from the database following the elimination of endogenous and exogenous contaminants and following the masking of repeats.

#### **EXAMPLE 8**

#### Measurement of Sequencing Accuracy by Comparison to Known Sequences

To further determine the accuracy of the sequencing procedure described in Example 6, the sequences of 5' ESTs derived from known sequences were identified and compared to the original known sequences. First, a FASTA analysis with overhangs shorter than 5 bp on both ends was conducted on the 5' ESTs to identify those matching an entry in the public human mRNA database available at the time of filing the priority applications. The 5' ESTs which matched a known human 15 mRNA were then realigned with their cognate mRNA and dynamic programming was used to include substitutions, insertions, and deletions in the list of "errors" which would be recognized. Errors occurring in the last 10 bases of the 5' EST sequences were ignored to avoid the inclusion of spurious cloning sites in the analysis of sequencing accuracy. This analysis revealed that the sequences incorporated in the database had an accuracy of more than 99.5%.

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#### **EXAMPLE 9**

#### Determination of Efficiency of 5' EST Selection

To determine the efficiency at which the above selection procedures isolated 5' ESTs which included sequences close to the 5' end of the mRNAs from which they derived, the sequences of the 25 ends of the 5' ESTs derived from the elongation factor 1 subunit α and ferritin heavy chain genes were compared to the known cDNA sequences of these genes. Since the transcription start sites of both genes are well characterized, they may be used to determine the percentage of derived 5' ESTs which included the authentic transcription start sites. For both genes, more than 95% of the obtained 5' ESTs actually included sequences close to or upstream of the 5' end of the corresponding mRNAs.

To extend the analysis of the reliability of the procedures for isolating 5' ESTs from ESTs in the database, a similar analysis was conducted using a database composed of human mRNA sequences extracted from GenBank database release 97 for comparison. The 5' ends of more than 85% of 5' ESTs derived from mRNAs included in the GenBank database were located close to the 5' ends of the known sequence. As some of the mRNA sequences available in the GenBank database are deduced from 35 genomic sequences, a 5' end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of ESTs including the authentic 5' ends of their corresponding mRNAs.

#### **EXAMPLE 10**

#### Calculation of Novelty Indices for 5'EST Libraries

In order to evaluate the novelty of 5'EST libraries, the following analysis was performed. For each sequenced 5'EST library, the sequences were clustered by the 5' end. Each sequence in the library was compared to the others and the longest sequence found in the cluster was used as representative of the group. A novelty rate (NR) was then defined as: NR= 100 X (Number of new unique sequences found in the library/Total number of sequences from the library). Typically, novelty rating ranged between 10% and 41% depending on the tissue from which the 5'EST library was obtained. For most of the libraries, the random sequencing of 5' EST libraries was pursued until the novelty rate reached 20%.

#### **EXAMPLE 11**

#### Generation of Consensus Contigated 5' ESTs

Since the cDNA libraries made above include multiple 5' ESTs derived from the same mRNA, overlapping 5'ESTs may be assembled into continuous sequences. The following method describes how to efficiently align multiple 5'ESTs in order to yield not only consensus contigated 5'EST sequences for mRNAs derived from different genes but also consensus contigated 5'EST sequences for different mRNAs, so called variants, transcribed from the same gene such as alternatively spliced mRNAs.

The whole set of sequences was first partitioned into small clusters containing sequences
which exhibited perfect matches with each other on a given length and which derived from a small number of different genes. Some 5'EST sequences, so called singletons, were not aligned using this approach because they were not homologous to any other sequence.

Thereafter, all variants of a given gene were identified in each cluster using a proprietary software. 5'EST sequences belonging to the same variant were then contigated and consensus contigated 5'EST sequences generated for each variant. All consensus contigated 5' EST sequences were subsequently compared to the whole set of individual 5'EST sequences used to obtained them.

If desired, the consensus contigated 5'EST sequences may be verified by identifying clones in nucleic acid samples derived from biological tissues, such as cDNA libraries, which hybridize to the probes based on the sequences of the consensus contigated 5'ESTs using any methods described herein and sequencing those clones.

Application of this alignment method to a selected set of 5'ESTs free from endogenous contaminants and uninformative sequences, and following the masking of repeats, yielded consensus contigated 5'EST sequences or variants of clustered genes encompassing many individual 5'ESTs. Both non aligned 5'ESTs, i.e. singletons, and consensus contigated 5'ESTs were then compared to already known sequences and those sequences matching human mRNA sequences were eliminated from further analysis.

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## EXAMPLE 12

#### Identification of Open Reading Frames in 5' ESTs

Subsequently, consensus contigated 5'ESTs and 5'ESTs were screened to identify those having an open reading frame (ORF).

5 Such open reading frames were simply defined as uninterrupted nucleic acid sequences longer than 45 nucleotides and beginning with an ATG codon.

Alternatively, the nucleic acid sequence was first divided into several subsequences which coding propensity was evaluated separately using one or several different methods known to those skilled in the art such as the evaluation of N-mer frequency and its variants (Fickett and Tung, 10 Nucleic Acids Res; 20:6441-50 (1992)) or the Average Mutual Information method (Grosse et al., International Conference on Intelligent Systems for Molecular Biology, Montreal, Canada, June 28-July 1, 1998). Each of the scores obtained by the techniques described above were then normalized by their distribution extremities and then fused using a neural network into a unique score that represents the coding probability of a given subsequence. The coding probability scores obtained for 15 each subsequence, thus the probability score profiles obtained for each reading frame, was then linked to the initiation codons present on the sequence. For each open reading frame, defined as a nucleic acid sequence beginning with an ATG codon, an ORF score was determined. Preferably, this score is the sum of the probability scores computed for each subsequence corresponding to the considered ORF in the correct reading frame corrected by a function that negatively accounts for 20 locally high score values and positively accounts for sustained high score values. The most probable ORF with the highest score was selected.

In some embodiments, nucleic acid sequences encoding an "incomplete ORF", as referred therein, namely an open reading frame in which a start codon has been identified but no stop codon has been identified, were obtained.

In other embodiments, nucleic acid sequences encoding a "complete ORF", as used therein, namely an open reading frame in which a start codon and a stop codon have been identified, are obtained.

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In a preferred embodiment, open reading frames encoding polypeptides of at least 50 amino acids were obtained.

To confirm that the chosen ORF actually encodes a polypeptide, the consensus contigated 5'EST or 5'EST may be used to obtain an extended cDNA using any of the techniques described therein, and especially those described in Examples 19 and 20. Then, such obtained extended cDNAs may be screened for the most probable open reading frame using any of the techniques described therein. The amino acid sequence of the ORF encoded by the consensus contigated 5'EST or 5'EST may then be 35 compared to the amino acid sequence of the ORF encoded by the extended cDNA using any of the algorithms and parameters described therein in order to determine whether the ORF encoded by the extended cDNA is basically the same as the one encoded by the consensus contigated 5'EST or 5'EST.

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Alternatively, to confirm that the chosen ORF actually encodes a polypeptide, the consensus contigated 5'EST or 5'EST may be used to obtain an extended cDNA using any of the techniques described therein, and especially those described in Examples 19 and 20. Such an extended cDNA may then be inserted into an appropriate expression vector and used to express the polypeptide encoded by 5 the extended cDNA as described therein. The expressed polypeptide may be isolated, purified, or enriched as described therein. Several methods known to those skilled in the art may then be used to determine whether the expressed polypeptide is the one actually encoded by the chosen ORF, therein referred to an the expected polypeptide. Such methods are based on the determination of predictable features of the expressed polypeptide, including but not limited to its amino acid sequence, its size or its 10 charge, and the comparison of these features to those predicted for the expected polypeptide. following paragraphs present examples of such methods.

One of these methods consists in the determination of at least a portion of the amino acid sequence of the expressed polypeptide using any technique known to those skilled in the art. For example, the amino-terminal residues may be determined using techniques either based on Sanger's 15 technique of acid hydrolysis of a polypeptide which N-terminal residue has been covalently labeled or using techniques based on Edman degradation of polypeptides which N-terminal residues are sequentially labeled and cleaved from the polypeptide of interest. The amino acid sequence of the expressed polypeptide may then be compared to the one predicted for the expected polypeptide using any algorithm and parameters described therein.

Alternatively, the size of the expressed polypeptides may be determined using techniques familiar to those skilled in the art such as Coomassie blue or silver staining and subsequently compared to the size predicted for the expected polypeptide. Generally, the band corresponding to the expressed polypeptide will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that 25 expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, specific antibodies or antipeptides may be generated against the expected polypeptide as described in Example 34 and used to perform immunoblotting or immunoprecipitation studies against the expressed polypeptide. The presence of a band in samples from cells containing the expression vector with the extended cDNA which is absent in samples from cells containing the 30 expression vector encoding an irrelevant polypeptide indicates that the expected polypeptide or portion thereof is being expressed. Generally, the band corresponding to the expressed polypeptide will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage

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The 5'ESTs or consensus contigated 5'ESTs found to encode an ORF were then searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, Nucleic Acids Res. 14:4683-4690, 1986. Those sequences encoding a 15 amino acid long stretch with a score of at least 3.5 in the Von Heijne signal peptide identification matrix were considered to possess a signal sequence. Those nucleic acid sequences which match a known human mRNA or EST sequence and have a 5' end located downstream of the known 5' end, preferably by more than 20 nucleotides, were excluded from further analysis. The remaining nucleic acids having signal sequences therein were included in a database called SignalTag<sup>TM</sup>.

10 EXAMPLE 14

Confirmation of Accuracy of Identification of Potential Signal Sequences in 5' ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino acids located at the N terminus of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5' region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in Figure 2.

Using the above method of identification of secretory proteins, 5' ESTs of the following polypeptides known to be secreted were obtained: human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase

25 precursor. Thus, the above method successfully identified those 5' ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5' ESTs or consensus contigated 5' ESTs actually functions as a signal peptide, the signal sequences from the 5' ESTs or consensus contigated 5' ESTs may be cloned into a vector designed for the identification of signal peptides. Such vectors are designed to confer the ability to grow in selective medium only to host cells containing a vector with an operably linked signal sequence. For example, to confirm that a 5' EST or consensus contigated 5' EST encodes a genuine signal peptide, the signal sequence of the 5' EST or consensus contigated 5' EST may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors with the correctly inserted 5' EST or consensus contigated 5' EST signal sequence confirms that the 5' EST or consensus contigated 5' ESTs encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the extended cDNAs obtained using the ESTs or consensus contigated 5' ESTs into expression vectors such as pXT1 as described below, or by constructing promoter-signal sequence-reporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After introduction of these 5 vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the medium from control cells containing vectors lacking the signal sequence or extended cDNA insert to identify vectors which encode a functional signal peptide or an authentic secreted protein.

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#### **EXAMPLE 15**

#### Analysis of the Sequences of the Invention

The set of the nucleic acid sequences of the invention (SEQ ID NOs.24-811 and 1600-1622) was obtained as described in Example 11. Subsequently, the most probable open reading frame was 15 determined and signal sequences were searched, as described in Examples 12 and 13, for all sequences of the invention.

The nucleotide sequences of the SEQ ID NOs. 24-811 and 1600-1622 and the polypeptides sequences encoded by SEQ ID NOs. 24-811 (i.e. polypeptide sequences of SEQ ID NOs. 812-1599) are provided in the appended sequence listing which structure is as follows.

SEO ID NOs. 24-728 are nucleic acids having an incomplete ORF which encodes a signal peptide. The locations of the incomplete ORFs and sequences encoding signal peptides are listed in the accompanying Sequence Listing. In addition, the von Heijne score of the signal peptide computed as described in Example 13 is listed as the "score" in the accompanying Sequence Listing. The sequence of the signal-peptide is listed as "seq" in the accompanying Sequence Listing. The "/" in the signal peptide 25 sequence indicates the location where proteolytic cleavage of the signal peptide occurs to generate a mature protein.

SEQ ID NOs. 729-765 are nucleic acids having an incomplete ORF in which no sequence encoding a signal peptide has been identified to date. However, it remains possible that subsequent analysis will identify a sequence encoding a signal peptide in these nucleic acids. The locations of the 30 incomplete ORFs are listed in the accompanying Sequence Listing.

SEO ID NOs. 766-792 are nucleic acids having a complete ORF which encodes a signal peptide. The locations of the complete ORFs and of the signal peptides, the von Heijne score of the signal peptide, the sequence of the signal-peptide and the proteolytic cleavage site are indicated as described above.

SEO ID NOs. 793-811 are nucleic acids having a complete ORF in which no sequence encoding a signal peptide has been identified to date. However, it remains possible that subsequent analysis will

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identify a sequence encoding a signal peptide in these nucleic acids. The locations of the complete ORFs are listed in the accompanying Sequence Listing.

SEQ ID NOs. 812-1516 are "incomplete polypeptide sequences" which include a signal peptide. "Incomplete polypeptide sequences" are polypeptide sequences encoded by nucleic acids in which a start 5 codon has been identified but no stop codon has been identified. These polypeptides are encoded by the nucleic acids of SEQ ID NOs. 24-728. The location of the signal peptide, the von Heijne score of the signal peptide, the sequence of the signal-peptide and the proteolytic cleavage site are indicated as described above.

SEQ ID NOs. 1517-1553 are incomplete polypeptide sequences in which no signal peptide has 10 been identified to date. However, it remains possible that subsequent analysis will identify a signal peptide in these polypeptides. These polypeptides are encoded by the nucleic acids of SEQ ID NOs. 729-765.

SEO ID NOs. 1554-1580 are "complete polypeptide sequences" which include a signal peptide. "Complete polypeptide sequences" are polypeptide sequences encoded by nucleic acids in which a start 15 codon and a stop codon have been identified. These polypeptides are encoded by the nucleic acids of SEO ID NOs. 766-792. The location of the signal peptide, the von Heijne score of the signal peptide, the sequence of the signal-peptide and the proteolytic cleavage site are indicated as described above..

SEQ ID NOs. 1581-1599 are complete polypeptide sequences in which no signal peptide has been identified to date. However, it remains possible that subsequent analysis will identify a signal 20 peptide in these polypeptides. These polypeptides are encoded by the nucleic acids of SEQ ID NOs.793-811.

SEO ID NOs. 1600-1622 are nucleic acid sequences in which no open reading frame has been conclusively identified to date. However, it remains possible subsequent analysis will identify an open reading frame in these nucleic acids.

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In the accompanying Sequence Listing, all instances of the symbol "n" in the nucleic acid sequences mean that the nucleotide can be adenine, guanine, cytosine or thymine. In some instances the polypeptide sequences in the Sequence Listing contain the symbol "Xaa." These "Xaa" symbols indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where applicants believe one should not exist (if the sequence 30 were determined more accurately). In some instances, several possible identities of the unknown amino acids may be suggested by the genetic code.

In the case of secreted proteins, it should be noted that, in accordance with the regulations governing Sequence Listings, in the appended Sequence Listing, the full protein (i.e. the protein containing the signal peptide and the mature protein) extends from an amino acid residue having a 35 negative number through a positively numbered C-terminal amino acid residue. Thus, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid

number 1, and the first amino acid of the signal peptide is designated with the appropriate negative number.

If one of the nucleic acid sequences of SEQ ID NOs. 24-811 and 1600-1622 are suspected of containing one or more incorrect or ambiguous nucleotides, the ambiguities can readily be resolved by resequencing a fragment containing the nucleotides to be evaluated. If one or more incorrect or ambiguous nucleotides are detected, the corrected sequences should be included in the clusters from which the sequences were isolated, and used to compute other consensus contigated sequences on which other ORFs would be identified. Nucleic acid fragments for resolving sequencing errors or ambiguities may be obtained from deposited clones or can be isolated using the techniques described herein.

Resolution of any such ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or erroneous sequences. For example, the primers may hybridize to sequences within 50-75 bases of the ambiguity or error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences encoded by the DNA containing the error or ambiguity. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its sequence.

In addition, if one of the sequences of SEQ ID NOs. 812-1599 is suspected of containing a truncated ORF as the result of a frameshift in the sequence, such frameshifting errors may be corrected by combining the following two approaches. The first one involves thorough examination of all double predictions, i.e. all cases where the probability scores for two ORFs located on different reading frames are high and close, preferably different by less than 0.4. The fine examination of the region where the two possible ORFs overlap may help to detect the frameshift. In the second approach, homologies with known proteins are used to correct suspected frameshifts.

Of the identified clusters, some were shown to be multivariant, i.e. to contain several variants of the same gene. Table I gives for each of the multivariant clusters named by its internal reference (first column), the list of all variant consensus contigated 5'ESTs (second column), each being represented by a different sequence identification number.

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TABLE I

Cluster Internal Reference	SEQ ID NOs of Variants
C1	687, 791
C2	744, 798
C3	640, 811
C4	59, 66
C5	84, 97

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C6	287, 289
C7	286, 775, 777
C8	762, 768
C9	783, 784
C10	80, 1603
C11	655, 736
C12	805, 806

Table II provides a list preferred polynucleotide fragments which are derivatives of the consensus contigated 5'ESTs. As used herein the term "polynucleotide described in Table II" refers to the all of the preferred polynucleotide fragments defined in Table II in the following manner. The fragments are referred to by their SEQ ID numbers in the first column. The preferred polynucleotide fragments are then defined by a range of nucleotide positions from the SEQ IDs of the consensus contigated 5'ESTs as indicated in the second column entitled "positions of preferred fragments." The preferred polynucleotide fragments correspond to the individual 5'ESTs aligned to obtain the consensus contigated 5'EST and to those filed in the priority documents. The third column entitled "variant nucleotides" describes the nucleotide sequence variations observed between the consensus contigated 5'EST and preferred nucleic acid fragments as follows:

A) Substitutions in the sequence of a consensus contigated 5'EST to derive a preferred polynucleotide fragment are denoted by an "S", followed by a number indicating the first nucleotide position in a specific SEQ ID to be substituted in a string of substituted nucleotides or the position of the substituted nucleotide in the case of a single substituted nucleotide. Then there is a coma followed by one or more lower case letters indicating the identity of the nucleotide(s) occurring in the substituted position(s). For example, SEQ ID NO: 3401; Position of preferred fragments: 1-250; Variant nucleotides S45, atc would indicate that a preferred polynucleotide fragment had the sequence of positions 1 to 250 of SEQ ID NO. 3401, except that the nucleotides at positions 45, 46, and 47 were substituted with A, T, and C, respectively, in the preferred polynucleotide as compared with the sequence of SEQ ID No. 3401.

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B) Insertions in the sequence of a consensus contigated 5'EST to derive a preferred polynucleotide fragment are denoted by an "I", followed by a number indicating the nucleotide position in a specific SEQ ID after which a string of nucleotides is inserted or the position after which the nucleotide is inserted in the case of a single inserted nucleotide. Then there is a coma followed by one or more lower case letters indicating the identity of the nucleotide(s) occurring in the inserted position(s). For example, SEQ ID NO: 7934; Position of preferred fragments: 1-500; Variant nucleotides: 136,gataca would indicate that a preferred polynucleotide fragment had the sequence of positions 1 to 500 of SEQ ID NO. 7934, except that after the nucleotides at position 36 a GATACA string of nucleotides is inserted in the preferred polynucleotide as compared with the sequence of SEQ ID No. 7934.

C) Deletions in the sequence of a consensus contigated 5'EST to derive a preferred nucleic acid fragment are denoted by an "D", followed by a number indicating the first nucleotide position in a specific SEQ ID to be deleted in a string of deleted nucleotides or the position of the deleted nucleotide in the case of a single deleted nucleotide. Then there is a coma followed by number indicating the number of nucleotide(s) deleted from the sequence provided in the sequence ID. For example, SEQ ID NO: 5398; Position of preferred fragments: 56-780; Variant nucleotides D114,5 would indicate that a preferred polynucleotide fragment had the sequence of positions 56 to 780 of SEQ ID NO. 5398, except that the nucleotides in positions 114 to 118 had been deleted in the preferred polynucleotide as compared with the sequence of SEQ ID No. 5398.

The present invention encompasses isolated, purified, or recombinant nucleic acids which consist of, consist essentially of, or comprise a contiguous span of at least 8, 10, 12, 15, 18, 20, 25, 35, 40, 50, 70, 80, 100, 250, or 500 nucleotides in length, to the extent that a contiguous span of these lengths is consistent with the lengths of the particular polynucleotide, of a polynucleotide described in Table II, or a sequence complementary thereto, wherein said polynucleotide described in Table II is selected individually or in any combination from the polynucleotides described in Table II. The present invention also encompasses isolated, purified, or recombinant nucleic acids which consist of or consist essentially of a polynucleotide described in Table II, or a sequence complementary thereto, wherein said polynucleotide is selected individually or in any combination from the polynucleotides described in Table II. The present invention further encompasses isolated or purified polypeptides which consist of, consist essentially of, or comprise a contiguous span of at least 8, 10, 12, 15, 18, 20, 25, 35, 40, 50, 70, 80, or 100 amino acids encoded by a polynucleotide described in Table II.

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Table II

SEQ ID NO.	Positions of Preferred Fragments	Variant nucleotides
35	1-423	S124, s; I135, a; S293, w; I363, a; S377, r; D424, 15
41	1-427	I117, m; S120, r; S124, g; D373, 1; S376, b; S378, b; I427, gggg; D428, 109
43	1-276	S114, m; S118, rg; S123, r; S139, nr; I142, t; D148, 1; D152, 1; I228, t; I276, gg; D277, 136
45	126-420	D1, 125; I420, ggg; D421, 100
46	1-255	S139, r; I145, r; S146, mm; S150, ar; S254, g; D256, 128
48	4-437	D1, 3; S49, a, S55, g; S79, a; S90, a; I437, tetetg
59	1-471	S26, a; S44, t; S48, t; S109, a; S191, t; S200, gc; S203, a; S210, g; S237, a; S240, g; S255, a; S272, a; S277, a; S279, a; S284, t; S297, g; S305, g; S316, a; I471, ggtca
66	1-428	I428, tactgggg

82	1-399	S251, t; S277, d; I399, aagccggg
84	5-488	D1, 4; S210, g; S293, a; S325, g; S339, a;
		S348, g; S353, g; S395, g; I488, cacca
93	1-508	I508, gattt
96	26-315	D1, 25; S28, a; S62, c; I315, cagatgg
97	4-460	D1, 3; S19, g; S31, g; S114, gt; S118, a; S123,
į.		tc; S127, c; S132, a; S186, g; S190, c; S203, t;
		S210, g; S232, c; I460, acgtt
105	1-281	S273, a; I281, g; D282, 211
114	10-315	I0, t; D1, 9; S91, m; S267, n; S276, w; S292, h; S295, m; I315, tggg; D316, 19
118	1-145	S57, d; S126, d; I145, ccctc
120	2-348	D1, 1; S104, t; I348, g; D349, 38
121	1-190	I121, c; I190, ccctt
123	1-353	II17, m; I186, w; S187, y; I353, caccgggg
124	1-249	1249, ggrvgggg
125	114-375	D1, 113; S206, wn; I231, a; I375, ccctagg
126	1.437	S297, cc; S307, tg; S312, a; S318, g; S341, a;
120	1. 43/	S351, t; S353, g; S383, c; S387, a; D404, 1
136	82-428	D1, 81; I428, aaagtg
139	1-268	I268, gggaaggg
148	6-405	D1, 5; I405, ggtgt
159	1-230	S227, ta; I230, ccctggg
165	3-256	10, tat; D1, 2; I17, c; S18, t; S111, d; I115, t;
105	3-230	S123, r; I256, aaggeggg
170	1-280	I103, t; S104, c; I111, t; I280, cgttcggg
194	1-215	S50, s; S186, sn; S199, k; I215, gcagcggg
213	1-158	S128, m; I132, w; S143, d; I158, tgcccggg
223	3-431	D1, 2; S28, s; S79, c; S82, s; S308, nr; S328,
		nb; I431, ccggc
247	1-359	I76, gttt; I359, tccctgg
258	1-236	S72, r; S81, g; S197, s; I205, ss; S232, k; I236,
		actteggg
264	5-283	D1, 4; S64, g; S122, m; S134, yy; I137, c;
		I151, t; I283, gttgc
269	1-143	S111, s; I143, ggggcggg
286	5-207	D1, 4; S204, a; S206, c; I207, gg; D208, 567
287	1-277	S114, r; I125, t; S131, ag; S256, tg; S259, tt;
		S262, at; S267, t; S269, c; S273, c; I277,
		ccggg; D278, 337
289	69-416	D1, 68; 1416, agccaggg
289	1-278	S114, r; I125, t; S131, ag; S277, c; I278, cggg;
	1	D279, 138
292	20-254	D1, 19; I254, aaagagg
293	1-414	I414, tagcag
300	1-285	S16, m; S67, y; I285, baccacggg; D286, 1
349	23-431	D1, 22; I118, a; S214, y; I431, caactgg
350	3-386	D1, 2; S42, w; 1263, c; I386, gggat
368	3-446	D1, 2; I446, tctct
385	1-193	135, t; 1108, t; 1134, r; S135, a; S137, r; S143,
	1_	w; I178, c; I193, gagcgggg
411	6-391	D1, 5; S17, r; S27, t; S334, y; D392, 244
412	1-185	S49, s; S127, s; I185, gctggg; D186, 150
		1

	r	33
415	2-229	D1, 1; S3, a; I229, caaatggg
435	1-386	S4, s; I386, ccggg
436	4-472	D1, 3; S61, sa; D238, 1; S239, s; I472, agtgtgg
437	1-340	1340, ggg; D341, 129
441	1-409	S109, smag; I409, cgcacggg
454	1-492	S72, nn; S115, t; S121, bwy; S181, yn; I492, gagtc
455	1-177	114, w; 116, a; 1177, gagctggg
459	1-311	S39, n; S74, rg; I311, accatggg
460	1-425	1425, agtac
461	5-420	D1, 4; I420, tegte
481	1-429	I10, w; S262, d; S333, n; I429, ctccaggg
489	1-414	D72, 1; S117, n; S396, d; I414, ggaca
496	1-215	1215, ttttcggg
501		
	1-430 91-413	S275, n; I430, aggat
502	<del></del>	D1, 90; 1413, aaacgggg
504	21-420	D1, 20; S47, w; S83, n; I280, n; S281, na; S292, v; S314, sm; S368, ww; S373, w; I420,
	10.457	cccca
505	18-457	D1, 17; D36, 1; S182, g; S273, n; S283, a;
	1 202	S416, bh; I457, ctcga
514	1-303	1303, accca
515	1-455	S11, t; I12, n; S30, r; S256, wr; I333, t; I455, cataa
517	24-453	D1, 23; I453, agagcggg
519	1-275	I119, gt; S125, w; I129, w; S133, k; S137, k; S167, k; I275, gcccc
522	1-313	I313, agcgtggg
526	4-366	I0, t; D1, 3; I366, ggcccggg
530	1-434	S328, g; I434, aagat
535	1-379	S128, g; S162, m; D380, 5
561	2-341	D1, 1; I341, raagagg
568	1-246	I118, g; S137, g; I246, aaaccggg
570	1-207	I207, ttttt
576	1-288	134, c; 1288, cccgtgg
588	1-390	S218, a; S224, k; S314, dh; S358, s; D376, 1;
		1390, atg; D391, 23
597	31-274	D1, 30; S49, n; I274, tccatgg
606	1-354	1141, g; D174, 1; S229, π; D355, 72
627	1-415	S7, a; I415, cattt
634	1-178	D179, 212
640	6-428	D1, 5; D429, 79
641	64-483	D1, 63; I165, d; D183, 1; S185, y; S253, t;
·		D279, 2; S416, a; I483, atata
655	1-280	S58, c; I84, g; S88, k; S204, ac; S244, g; S247,
}		g; 1280, ggg; D281, 90
672	34-489	D1, 33; S316, k; S331, k; S333, w; S486, g; S488, c; D490, 4
687	116-473	D1, 115; S142, n; I473, cctcgggg
697	1-202	S142, s; S144, sr; S148, d; S152, d; I155, a;
	<u> </u>	1164, a; S174, k; 1202, gcc; D203, 291
708	8-384	D1, 7; S104, b; 1384, gaaaa
710	1-167	S40, k; S49, db; I167, tatct

722	1-191	1125, c; 1191, ttttt
723	1-316	1316, aggg; D317, 157
729	15-373	D1, 14; S139, t; I373, cgcag; D374, 99
730	29-372	D1, 28; I155, g; S192, ka; S333, d; I372, m;
		D373, 93
731	1-290	S10, kk; S30, b; S32, t; S92, t; S197, dy; S278,
		g; 1290, aggg; D291, 55
732	8-277	D1, 7; I113, a; S127, w; I131, s; S132, r; S156,
		w; S160, r; S211, n; S215, w; I247, a; D278,
		121
733	20-375	D1, 19; S306, sbs; I325, h; S326, nr; S338,
		ywd; S344, v; I375, aggg; D376, 68
734	1-359	D66, 1; D360, 14
735	25-322	D1, 24; S30, r; I193, a; I322, ccaaggg
736	9-181	D1, 8; S58, g; I181, aactaggg
737	1-160	S97, ta; 1160, aggtc
738	1-227	D228, 7
739	45-514	D1, 44; S178, s; I182, c; S436, dmn; S461, v;
-		S476, c; S506, t; D515, 75
740	11-388	D1, 10; I388, cgacaggg
741	1-478	S118, s; S125, a; I126, s; S134, k; S421, vn;
		I478, aatsc
742	217-553	I0, tt; D1, 216; S286, r; S294, m; S311, r;
		S317, s; S338, r; S442, dm; S469, h; S476, r;
		S485, s; S491, w; I495, ht; S496, v; S513, r;
		D521, 1; S536, m; D554, 199
743	1-459	II 1, s; S258, m; I270, m; I304, c; I308, amta;
		S313, c; S438, v; I459, agggag
744	25-316	D1, 24; S315, g; D317, 95
745	21-283	D1, 20; 140, g; S41, c; D123, 1; S181, sr; S227,
		r; I283, ccgcg; D284, 121
746	1-256	D257, 173
747	1-179	S134, w; S138, w; S140, kt; I179, cacca
748	1-235	S46, t; 172, t; S189, cc; S222, c; D236, 148
749	2-370	D1, 1; S32, cg; D144, 1; S341, g; D371, 76
750	18-410	10, aag; D1, 17; 1410, aatcc
751	22-355	D1, 21; D148, 1; S150, c; S152, a; S313, n;
		D356, 181
752	1-139	S50, t; I118, g; I139, ccct
753	1-189	S26, r; S115, s; I121, r; S122, r; S128, s; S143,
		r; I146, w; S156, r; D190, 4
754	1-395	S212, wd; 1395, cggca
755	19-460	D1, 18; S26, c; S156, a; S253, n; 1460, tagaagg
756	2-142	D1, 1; I106, gc; S107, t; S110, c; I142,
		ccaccggg
757	28-296	D1, 27; I119, s; I122, t; S128, s; S255, t; S267,
		m; D297, 66
758	11-368	D1, 10; 1200, g; S201, c; S281, d; S317, c;
		1368, ccatcggg
759	19-452	D1, 18; S421, w; I452, a
760	25-175	D1, 24; S34, yk; 1175, ccggg; D176, 120
761	1-212	1212, cactoggg
762	1-374	S320, s; S349, a; D375, 249
763	8-152	D1, 7; I152, acggg; D153, 109
	U-132	21, 1, 1132, 40666, 2133, 103

	<del></del>	33
764	1-160	I127, g; I145, g; I160, cgcccggg
765	137-313	D1, 136; S272, m; I279, s; S310, t; I313, ggg;
		D314, 203
766	1-320	S278, ag; S281, cagacc; S288, ta; S291, caag;
		S296, c; S317, m; I320, cggg; D321, 306
767	6-336	10, aa; D1, 5; S149, w; S245, y; D337, 137
768	1-374	S320, s; D375, 299
769	53-435	D1, 52; S59, b; S344, nnkw; D436, 104
770	24-448	D1, 23; S25, g; S411, w; S416, m; D449, 31
771	1-370	S3, c; S180, m; S275, r; D371, 122
772	1-388	I299, c; S326, c; D389, 8
773	1-143	S18, c; S66, a; I143, ggg; D144, 274
774	1-347	S194, a; S205, c; I347, ggg; D348, 107
775 .	5-207	D1, 4; S111, tg; S158, g; S171, c; S191, a;
	<u> </u>	S204, a; S206, c; I207, gg; D208, 324
776	1-368	I200, c; S201, a; S291, ta; I332, c
777	5-207	D1, 4; S204, a; S206, c; I207, gg; D208, 262
778	39-342	D1, 38; S184, r; D343, 126
779	4-360	D1, 3; S13, m; S15, c; S22, s; S24, m; S48, r;
		S56, s; S335, c; S345, rs; I360, ggg; D361, 119
780	1-472	I347, c; D473, 32
781	116-426	D1, 115; S219, m; S424, g; D427, 118
782	1-391	S386, k; D392, 64
783	1-453	D109, 1; S110, y; S125, y; I128, g; S132, k;
704	20.404	1453, ctctc
784	29-494	D1, 28; S72, r; D495, 93
785	99-461	D1, 98; S218, r; I461, gaccgggg
786	2-465	D1, 1; S8, y; S388, s; I398, g; S400, t; S403, at; S417, g; D466, 24
787	28-271	D1, 27; S99, t; S230, c; S266, ga; S269, c;
'0'	20 27.	I271, g; D272, 126
788	1-285	D280, 1; I285, g; D286, 310
789	1-209	S205, c; D210, 150
790	51-297	D1, 50; I297, ggggg; D298, 539
791	113-327	D1, 112; S218, g; I226, g; D280, 1; I327,
		cgcaggg; D328, 224
792	17-218	D1, 16; S58, t; S217, t; I218, gggg; D219, 219
793	11-92	D1, 10; S91, c; I92, a; D93, 258
794	9-431	D1, 8; I431, taagt
795	30-341	D1, 29; I341, a; D342, 175
796	1-442	S17, w; S19, wr; D35, 1; S134, t; S264, n;
		S322, nr; S369, s; S420, s; S422, y; I442,
		tcctcggg
797	1-420	S136, c; S150, c; I245, ccc; I420, ggagtg
798	25-316	D1, 24; S315, g; D317, 97
799	1-344	D345, 57
800	7-465	D1, 6; S59, k; S146, a; S186, krn; 1465, gttca
801	121-422	D1, 120; 1269, c; S419, cc; I422, gg; D423, 207
802	46-477	D1, 45; S132, bn; I477, actac
802	15-467	D1, 14; S45, k; S65, t; S418, ys; D452, 1;
003	13-40/	D468, 119
804	1-341	S42, t; S97, d; S326, gtg; S331, tgt; S336, a;

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		S338, c; I341, cccccggg; D342, 218
805	2-409	D1, 1; S334, d; I409, aggg; D410, 161
806	5-384	D1, 4, I384, actaa
807	1-301	S113, a; S117, c; S123, t; D128, 1; D134, 1;
		S282, g; S284, a; I301, gacggagggg; D302, 70
808	2-314	D1, 1; S306, g; I314, ggg; D315, 121
809	1-394	S53, g; S228, n; S272, vk; I301, g; I358, m;
		S368, nb; S375, w; I383, mm; I388, yt; I394,
	<u> </u>	nhaceggg
810	6-205	I0, a; D1, 5; I141, t; I205, ggg; D206, 630
811	6-270	D1, 5; I270, gggg; D271, 115
1600	1-247	S45, m; S114, k; I122, m; S123, yc; S158, rr;
		S221, k; I247, ccccaggg
1601	1-225	S109, bm; S195, m; I225, tgcacggg
1602	23-245	D1, 22; D138, 1; S139, s; S242, t; S244, g;
	,	1245, g; D246, 13
1603	1-303	S71, c; D277, 1; I303, ggagggg; D304, 38
1604	1-242	S47, w; S50, c; S81, h; S85, d; S91, k; S106, r;
<u> </u>		I242, tgtggg; D243, 50
1605	2-225	D1, 1; S20, k; S91, c; I225, ggg, D226, 132
1606	15-293	D1, 14; S156, g; S193, g; I200, t; I293,
		acaaaggg
1607	1-361	S323, c; 1361, cccca
1608	1-151	I151, taagggg; D152, 154
1609	1-242	S55, s; 1135, a; S152, h; 1242, cagtaggg
1610	1-196	I151, w; S190, k; I196, cctgtgg
1611	1-228	S115, k; S174, rk; I228, cgtttggg
1612	1-221	S108, v; 1221, tgatcggg
1613	1-281	I66, w; I137, a; D282, 79
1614	1-171	S53, k; S76, k; I80, k; S81, kw; S86, r; S92, k;
1616		S126, k; 1171, gccgagg
1615	2-193	D1, 1; S67, c; I121, s; S122, mm; S126, g;
1616	1.240	S130, r; S146, r; S156, gm; I193, cctca
1616	1-349	S251, ww; S259, rs; S275, k; I279, w; S285, y;
		S292, y; I320, m; I331, m; I338, w; I341, s;
1617	1 120	I349, accceggg
1617	1-129	I118, t; D130, 26
1618	1-184	D9, 1; D185, 1
1619	1-169	I122, t; I169, gcccaggg
1620	1-187	S106, k; S118, m; S122, cg; S132, k; D188, 59
1621	1-153	D125, 1; I131, ttt; S152, t; I153, gg; D154, 127
1622	1-400	S43, s; I126, g; I129, y; S353, d; I400, tatat

## **EXAMPLE 16**

## Categorization of 5' ESTs and Consensus Contigated 5'ESTs

The nucleic acid sequences of the present invention (SEQ ID NOs. 24-811 and 1600-1622) were grouped based on their homology to known sequences as follows. All sequences were compared to EMBL release 57 and daily releases available at the time of filing using BLASTN. All matches with a minimum of 25 nucleotides with 90% homology were retrieved and used to compute Tables IV and V.

In some embodiments, 5'ESTs or consensus contigated 5'ESTs nucleic acid sequence do not match any known vertebrate sequence nor any publicly available EST sequence, thus being completely new.

In other embodiments, 5'ESTs or consensus contigated 5'ESTs match a known sequence.

- Tables III and IV gives for each sequence of the invention in this category referred to by its sequence identification number in the first column, the positions of their preferred fragments in the second column entitled "Positions of preferred fragments." As used herein the term "polynucleotide described in Table III" refers to the all of the preferred polynucleotide fragments defined in Table III in this manner, and the term "polynucleotide described in Table IV" refers to the all of the preferred polynucleotides fragments defined in Table IV in this manner. The present invention encompasses isolated, purified, or recombinant nucleic acids which consist of, consist essentially of, or comprise a contiguous span of at least 8, 10, 12
  - nucleic acids which consist of, consist essentially of, or comprise a contiguous span of at least 8, 10, 12, 15, 18, 20, 25, 35, 40, 50, 70, 80, 100, 250, or 500 nucleotides in length, to the extent that a contiguous span of these lengths is consistent with the lengths of the particular polynucleotide, of a
- polynucleotide described in Table III or Table IV, or a sequence complementary thereto, wherein said

  polynucleotide described in Table III or Talbe IV is selected individually or in any combination from the
  polynucleotides described in Table III or Talbe IV. The present invention also encompasses isolated,
  purified, or recombinant nucleic acids which consist of or consist essentially of a polynucleotide
  described in Table III or Table IV, or a sequence complementary thereto, wherein said polynucleotide is

20

Table III

selected individually or in any combination from the polynucleotides described in Table III or Table IV.

SEQ ID	Positions of preferred
NO	fragments
24	1-251
25	1-83
28	227-276
29	1-27
- 30	130-242, 283-315, 365-461
32	314-399
33	89-321
34	1-38
35	1-52, 171-222
36	1-30, 408-441
37	1-138
39	115-140
40	1-97
41	1-112
42	1-177
46	1-38
48	376-400
51	400-466
54	1-259
55	189-320

	38
56	265-457
58	246-469
59	81-123, 418-444
60	1-348
61	78-123, 418-457
62	386-439
63	1-214
64	109-297
65	1-370
66	92-428
68	1-180
69	165-259
70	1-178
71	1-27
72	1-179
73	
75	1-65, 107-192
73 77	1-314
	263-388
78	1-64
79	1-149
80	101-142, 302-380
82	1-192
83	1-398
85	1-290
86	1-118, 149-336
87	1-262
88	1-149
89	1-315
90	1-74
91	1-335, 364-423
92	1-316
93	338-508
94	179-321
95	219-402
96	26-315
97	348-460
98	1-230
99	391-467
101	214-336
102	1-289
103	1-383
104	1-211
105	1-36
106	1-126
107	1-49
108	294-336
109	1-128
111	1-154
112	407-441
-113	1-80, 139-184
114	10-79
116	1-292
117	1-304

	39
119	1-288
120	2-348
121	1-122
123	188-353
124	1-249
125	295-375
128	1-244
129	1-232
130	196-312
131	178-276
132	37-174
133	1-344
. 134	1-244
135	1-217
136	82-428
137	1-29, 103-155, 274-434
138	1-395
139	1-268
140	1-170
141	1-396
142	1-73, 227-357
143	1-159
144	1-433
145	61-116
146	1-71, 179-205
147	177-300
149	1-146
151	1-166
152	1-382
153	1-208
154	121-251
155	1-147
157	1-115
158	1-175
159	1-44, 80-230
160	1-346
161	1-277
162	1-235
163	1-34
164	1-195
165	19-78, 175-217
166	1-209
	1-209
167	
168	128-218
169	49-245
170	179-280
171	1-103
172	1-218
173	1-380
174	1-139
175	1-122
176	1-300
177	1-466

	40
179	1-86
180	1-245
181	1-241
182	1-263
183	1-170
184	58-106, 399-443
185	1-427
186	1-365
187	
	1-260
188	1-172
189	1-150
190	161-271, 301-339
191	1-91
192	1-264
193	1-246
194	1-150
195	1-209
196	1-363
197	1-155
198	1-135
200	1-125
201	1-210
202	1-338
203	1-188
204	228-347
205	1-440
206	56-221
208	1-422
209	169-195
210	1-363
211	1-368
212	1-448
213	1-134
214	1-193
215	1-214
216	1-134
218	1-189
219	1-248
220	1-115
221	1-113
222	1-370
224	1-251
225	1-198
226	45-141
227	
	1-206
228	1-480
229	1-144
230	1-42, 281-351, 432-457
231	1-112
233	1-301
234	1-109
235	1-393
236	1-222

237         1-154           238         1-439           239         112-137           240         1-194           241         1-44           242         1-242           244         1-324           245         1-38, 217-280           246         1-60           247         77-359           248         1-236           249         1-342           250         80-382           251         1-303           252         62-259           253         1-165           254         1-328           255         1-320           256         1-305           257         1-181           258         116-174           259         1-265           260         1-272           261         1-62           263         1-371           266         1-274           267         1-342           268         364-427           269         31-143           270         1-79           271         1-113           275         1-254		41
239         112-137           240         1-194           241         1-44           242         1-242           244         1-324           245         1-38, 217-280           246         1-60           247         77-359           248         1-236           249         1-342           250         80-382           251         1-303           252         62-259           253         1-165           254         1-328           255         1-320           256         1-305           257         1-181           258         116-174           259         1-265           260         1-272           261         1-62           263         1-371           266         1-274           267         1-342           268         364-427           269         31-143           270         1-79           271         1-121           272         229-292           273         1-158           274         1-113	237	1-154
240         1-194           241         1-44           242         1-242           244         1-324           245         1-38, 217-280           246         1-60           247         77-359           248         1-236           249         1-342           250         80-382           251         1-303           252         62-259           253         1-165           254         1-328           255         1-320           256         1-305           257         1-181           258         116-174           259         1-265           260         1-272           261         1-62           263         1-371           266         1-274           267         1-342           268         364-427           269         31-143           270         1-79           271         1-121           272         229-292           273         1-158           274         1-113           275         1-254	238	1-439
241         1-44           242         1-242           244         1-324           245         1-38, 217-280           246         1-60           247         77-359           248         1-236           249         1-342           250         80-382           251         1-303           252         62-259           253         1-165           254         1-328           255         1-305           257         1-181           258         116-174           259         1-265           260         1-272           261         1-62           263         1-371           266         1-274           267         1-342           268         364-427           269         31-143           270         1-79           271         1-121           272         229-292           273         1-158           274         1-113           275         1-254           276         1-333           277         1-130	239	112-137
242         1-242           244         1-324           245         1-38, 217-280           246         1-60           247         77-359           248         1-236           249         1-342           250         80-382           251         1-303           252         62-259           253         1-165           254         1-328           255         1-320           256         1-305           257         1-181           258         116-174           259         1-265           260         1-272           261         1-62           263         1-371           266         1-274           267         1-342           268         364-427           269         31-143           270         1-79           271         1-121           272         229-292           273         1-158           274         1-113           275         1-254           276         1-333           277         1-130	240	1-194
242         1-242           244         1-324           245         1-38, 217-280           246         1-60           247         77-359           248         1-236           249         1-342           250         80-382           251         1-303           252         62-259           253         1-165           254         1-328           255         1-320           256         1-305           257         1-181           258         116-174           259         1-265           260         1-272           261         1-62           263         1-371           266         1-274           267         1-342           268         364-427           269         31-143           270         1-79           271         1-121           272         229-292           273         1-158           274         1-113           275         1-254           276         1-333           277         1-130	241	1-44
244       1-38, 217-280         246       1-60         247       77-359         248       1-236         249       1-342         250       80-382         251       1-303         252       62-259         253       1-165         254       1-328         255       1-320         256       1-305         257       1-181         258       116-174         259       1-265         260       1-272         261       1-62         263       1-371         266       1-274         267       1-342         268       364-427         269       31-143         270       1-79         271       1-121         272       229-292         273       1-158         274       1-113         275       1-254         276       1-333         277       1-130         278       1-184         279       1-265         280       1-188         281       1-177		
245         1-38, 217-280           246         1-60           247         77-359           248         1-236           249         1-342           250         80-382           251         1-303           252         62-259           253         1-165           254         1-328           255         1-320           256         1-305           257         1-181           258         116-174           259         1-265           260         1-272           261         1-62           263         1-371           266         1-274           267         1-342           268         364-427           269         31-143           270         1-79           271         1-121           272         229-292           273         1-158           274         1-113           275         1-254           276         1-333           277         1-130           278         1-184           279         1-265		
246       1-60         247       77-359         248       1-236         249       1-342         250       80-382         251       1-303         252       62-259         253       1-165         254       1-328         255       1-320         256       1-305         257       1-181         258       116-174         259       1-265         260       1-272         261       1-62         263       1-371         266       1-274         267       1-342         268       364-427         269       31-143         270       1-79         271       1-121         272       229-292         273       1-158         274       1-113         275       1-254         276       1-333         277       1-130         278       1-184         279       1-265         280       1-188         281       1-177         282       1-336         28		1-38, 217-280
247       77-359         248       1-236         249       1-342         250       80-382         251       1-303         252       62-259         253       1-165         254       1-328         255       1-320         256       1-305         257       1-181         258       116-174         259       1-265         260       1-272         261       1-62         263       1-371         266       1-274         267       1-342         268       364-427         269       31-143         270       1-79         271       1-121         272       229-292         273       1-158         274       1-113         275       1-254         276       1-333         277       1-130         278       1-184         279       1-265         280       1-188         281       1-177         282       1-336         283       1-294         2		
248       1-236         249       1-342         250       80-382         251       1-303         252       62-259         253       1-165         254       1-328         255       1-320         256       1-305         257       1-181         258       116-174         259       1-265         260       1-272         261       1-62         263       1-371         266       1-274         267       1-342         268       364-427         269       31-143         270       1-79         271       1-121         272       229-292         273       1-158         274       1-113         275       1-254         276       1-333         277       1-130         278       1-184         279       1-265         280       1-188         281       1-177         282       1-336         283       1-294         284       1-171		
249       1-342         250       80-382         251       1-303         252       62-259         253       1-165         254       1-328         255       1-320         256       1-305         257       1-181         258       116-174         259       1-265         260       1-272         261       1-62         263       1-371         266       1-274         267       1-342         268       364-427         269       31-143         270       1-79         271       1-121         272       229-292         273       1-158         274       1-113         275       1-254         276       1-333         277       1-130         278       1-184         279       1-265         280       1-188         281       1-177         282       1-336         283       1-294         284       1-171		<u> </u>
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504	1-63	

505         1-68           514         1-303           515         237-351           519         1-145           526         231-366           530         1-88           535         1-55           570         76-207           576         168-218, 261-288           588         1-331           597         1-83           627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139<		31
515         237-351           519         1-145           526         231-366           530         1-88           535         1-55           570         76-207           576         168-218, 261-288           588         1-331           597         1-83           627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28<	505	1-68
519         1-145           526         231-366           530         1-88           535         1-55           570         76-207           576         168-218, 261-288           588         1-331           597         1-83           627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           730         1-465           731         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28 <td>514</td> <td>1-303</td>	514	1-303
526         231-366           530         1-88           535         1-55           570         76-207           576         168-218, 261-288           588         1-331           597         1-83           627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115 <td>515</td> <td>237-351</td>	515	237-351
530         1-88           535         1-55           570         76-207           576         168-218, 261-288           588         1-331           597         1-83           627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62	519	1-145
535         1-55           570         76-207           576         168-218, 261-288           588         1-331           597         1-83           627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126	526	231-366
535         1-55           570         76-207           576         168-218, 261-288           588         1-331           597         1-83           627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126	530	1-88
570         76-207           576         168-218, 261-288           588         1-331           597         1-83           627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85	535	<del></del>
576         168-218, 261-288           588         1-331           597         1-83           627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           748         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40		<del></del>
588         1-331           597         1-83           627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148		<del></del>
597         1-83           627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134		
627         1-43           634         1-41           641         1-55, 334-483           672         1-34           687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531		<del></del>
634       1-41         641       1-55, 334-483         672       1-34         687       1-129         708       1-245, 296-384         710       1-26, 104-167         722       1-191         730       1-465         731       1-43         735       1-91         737       1-160         738       1-186         739       1-48         742       1-62, 99-248         743       1-315, 412-459         744       1-31         747       1-63         749       1-32         750       1-38         752       1-139         753       1-193         754       1-28         759       1-38         760       1-115         763       1-62         765       1-126         769       1-85         770       1-40         771       1-148         774       1-134         775       265-531         776       71-203         777       333-469         778       144-468	627	
641       1-55, 334-483         672       1-34         687       1-129         708       1-245, 296-384         710       1-26, 104-167         722       1-191         730       1-465         731       1-43         735       1-91         737       1-160         738       1-186         739       1-48         742       1-62, 99-248         743       1-315, 412-459         744       1-31         747       1-63         749       1-32         750       1-38         752       1-139         753       1-193         754       1-28         759       1-38         760       1-115         763       1-62         765       1-126         769       1-85         770       1-40         771       1-148         774       1-134         775       265-531         776       71-203         777       333-469         778       1-44-468         779       1-28		<del></del>
672       1-34         687       1-129         708       1-245, 296-384         710       1-26, 104-167         722       1-191         730       1-465         731       1-43         735       1-91         737       1-160         738       1-186         739       1-48         742       1-62, 99-248         743       1-315, 412-459         744       1-31         747       1-63         749       1-32         750       1-38         752       1-139         753       1-193         754       1-28         759       1-38         760       1-115         763       1-62         765       1-126         769       1-85         770       1-40         771       1-148         774       1-134         775       265-531         776       71-203         777       333-469         778       144-468         779       1-28         780       1-49		
687         1-129           708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28		
708         1-245, 296-384           710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49		<del></del>
710         1-26, 104-167           722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102	<del></del>	
722         1-191           730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59 <td< td=""><td></td><td></td></td<>		
730         1-465           731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59           783         1-53		
731         1-43           735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59           783         1-53           784         1-220, 262-390		<del></del>
735         1-91           737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59           783         1-53           784         1-220, 262-390		<u> </u>
737         1-160           738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59           783         1-53           784         1-220, 262-390		<del> </del>
738         1-186           739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59           783         1-53           784         1-220, 262-390		<u> </u>
739         1-48           742         1-62, 99-248           743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59           783         1-53           784         1-220, 262-390		<del></del>
742       1-62, 99-248         743       1-315, 412-459         744       1-31         747       1-63         749       1-32         750       1-38         752       1-139         753       1-193         754       1-28         759       1-38         760       1-115         763       1-62         765       1-126         769       1-85         770       1-40         771       1-148         774       1-134         775       265-531         776       71-203         777       333-469         778       144-468         779       1-28         780       1-49         781       1-102         782       1-59         783       1-53         784       1-220, 262-390		
743         1-315, 412-459           744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59           783         1-53           784         1-220, 262-390		
744         1-31           747         1-63           749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59           783         1-53           784         1-220, 262-390		
747       1-63         749       1-32         750       1-38         752       1-139         753       1-193         754       1-28         759       1-38         760       1-115         763       1-62         765       1-126         769       1-85         770       1-40         771       1-148         774       1-134         775       265-531         776       71-203         777       333-469         778       144-468         779       1-28         780       1-49         781       1-102         782       1-59         783       1-53         784       1-220, 262-390		
749         1-32           750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59           783         1-53           784         1-220, 262-390		
750         1-38           752         1-139           753         1-193           754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59           783         1-53           784         1-220, 262-390		
752     1-139       753     1-193       754     1-28       759     1-38       760     1-115       763     1-62       765     1-126       769     1-85       770     1-40       771     1-148       774     1-134       775     265-531       776     71-203       777     333-469       778     144-468       779     1-28       780     1-49       781     1-102       782     1-59       783     1-53       784     1-220, 262-390		
753     1-193       754     1-28       759     1-38       760     1-115       763     1-62       765     1-126       769     1-85       770     1-40       771     1-148       774     1-134       775     265-531       776     71-203       777     333-469       778     144-468       779     1-28       780     1-49       781     1-102       782     1-59       783     1-53       784     1-220, 262-390		
754         1-28           759         1-38           760         1-115           763         1-62           765         1-126           769         1-85           770         1-40           771         1-148           774         1-134           775         265-531           776         71-203           777         333-469           778         144-468           779         1-28           780         1-49           781         1-102           782         1-59           783         1-53           784         1-220, 262-390		
759     1-38       760     1-115       763     1-62       765     1-126       769     1-85       770     1-40       771     1-148       774     1-134       775     265-531       776     71-203       777     333-469       778     144-468       779     1-28       780     1-49       781     1-102       782     1-59       783     1-53       784     1-220, 262-390		
760     1-115       763     1-62       765     1-126       769     1-85       770     1-40       771     1-148       774     1-134       775     265-531       776     71-203       777     333-469       778     144-468       779     1-28       780     1-49       781     1-102       782     1-59       783     1-53       784     1-220, 262-390		
763     1-62       765     1-126       769     1-85       770     1-40       771     1-148       774     1-134       775     265-531       776     71-203       777     333-469       778     144-468       779     1-28       780     1-49       781     1-102       782     1-59       783     1-53       784     1-220, 262-390		
765     1-126       769     1-85       770     1-40       771     1-148       774     1-134       775     265-531       776     71-203       777     333-469       778     144-468       779     1-28       780     1-49       781     1-102       782     1-59       783     1-53       784     1-220, 262-390		
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771     1-148       774     1-134       775     265-531       776     71-203       777     333-469       778     144-468       779     1-28       780     1-49       781     1-102       782     1-59       783     1-53       784     1-220, 262-390		
774     1-134       775     265-531       776     71-203       777     333-469       778     144-468       779     1-28       780     1-49       781     1-102       782     1-59       783     1-53       784     1-220, 262-390		
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789	1-58	
791	1-126	
792	1-31, 129-220	
793	1-31	
794	355-431	
795	1-33	
<b>79</b> 7	1-31	
798	1-31	
799	1-401	
801	1-117	
802	1-92	
806	64-384	
807	1-331	
808	1-351	
810	1-39	
1600	1-25	
1603	1-341	
1606	1-31	
1607	1-361	
1608	164-305	
1611	85-228	
1612	1-221	
1613	112-360	
1614	1-171	
1615	94-193	
1617	1-155	
1620	1-246	

III. Evaluation of Spatial and Temporal Expression of mRNAs Corresponding to the 5'ESTs, Consensus Contigated 5'ESTs, or EST-related nucleic acids

## **EXAMPLE 17**

## Expression Patterns of mRNAs From Which the 5'ESTs were obtained

Each of the SEQ ID NOs. 24-811 and 1600-1622 was also categorized based on the tissue from which its corresponding mRNA was obtained, as follows.

Table V shows the spatial distribution of each nucleic acid sequence of the invention (SEQ ID NOs. 24-811 and 1600-1622) referred to by its sequence identification number in the first column. In the second column entitled tissue distribution, the spatial distribution is represented by the number of individual 5'ESTs used to assemble the consensus contigated 5'ESTs for a given tissue. Each type of tissue listed in Table V is encoded by a letter. The correspondence between the letter code and the tissue type is given in Table VI.

Table V

SEQ ID NO	Tissue Distribution	
24	AA:1	
25	S:1	
26	P:1	
27	W:1	
- 28	P:1	
29	S:1	
30	P:1	
31	P:1	
32	P:1	
33	P:1	
34	AB:1	
35	G:3; P:1; S:1; W:3; AA:4	
36	P:1	
37	S:1	
38	Q:1	
39	P:1	
40	AB:1	
41_	B:1; C:3; F:1; G:1; H:4; S:2; T:8; W:1; Z:1; AA:3; AC:1; AD:3	
42	A:1	
43	N:2	
44	P:1	
45	C:2; K:1; O:1; S:5	
46	K:1; S:2; AA:1	
47	AA:1	
48	C:1; O:1; P:8	
49	F.1	
50	P:1	
51	P:1	
52	S:1	
53	AA:1	
54	T:1	
55	P:1	
56	P:1	
57	P:1	
58	P:1	
59	P:7; T:2; Z:1	
60	R:1	
61	<u>[C:1]</u>	
62	P:1	
63	F:1	
64	AA:1	
65	F:1	

<b>6</b> 6	P:4; T:2; Z:1
67	S:1
68	AA:1
69	P:1
70	P:1
71	S:1
72	W:1
73	G:1
74	P:1
75	N:1
76	P:1
77	S:1
78	U:1
79	B:1
80	P:1
81	AC:1
82	K:1; O:1
83	G:1
84	C:1; K:2; P:29; S:2; T:1; X:2; Y:1; AA:2
85	K:1
86	C:1
87	F:1
88	AB:1
89	H:1
90	M:1
91	B:1
92	K:1
93	AC:2
94	P:1
95	M:1
96	Z:2
97	K:1; P:11; S:1; X:1; AA:1
98	W:1
99	X:1
100	P:1
101	AB:1
102	F:1
103	AA:1
104	K:1
105	B:4; C:6; E:2; H:3; O:2; Q:1; S:3; AC:2
106	T:1
107	0:1
108	P:1
109	G:1
110	AA:1
111	T:1 .
112	P:1
	F:1
113	]1.1

	55
. 114	B:3; C:4; K:5; S:4; Y:1
115	U:1
116	W:1
117	T:1
118	T:2
119	T:1
120	H:3
121	AA:3
122	K:1
123	H:2
124	AA:2
125	B:1; G:1; J:3; T:13; Y:5; AA:5; AD:2
126	U-1- D-1
127	K:1
128	F:1
129	G:1
130	P:1
	B:1
131	
	AA:1 W:1
133	
134	P:1
135	K:1
136	D.1, C.1
137	B:1
138	H:1
139	AC:2
140	T:1
141	B:1
142	H:1
143	T:1
144	H:1
145	D.1
146	R:1
147	P:1
148	C:1; H:2; O:1; S:2; T:1; AC:2
149	H:1
150	AA:1
151	W:1
152	S:1
153	F:1
154	M:1
155	B:1
156	R:1
157	W:1
158	T:1
159	C:1; AA:1
160	F:1
161	H:1

., • , , , , , , , , , , , , , , , , , ,	56	
162	D:1	
163	AA:1	
164	AA:1	
165	W:3	
166	AA:1	
167	W:1	
168	F:1	
169	B:1	-
170	G:2	
171	E:1	
172	B:1	
173	F:1	
174	B:1	
17.5	W:1	·
176	K:1	
177	AA:1	
178	S:1	
179	K:1	
180	AA:1	
181	W:1	
182	K:1	
183	T:1	
184	P:1	
185	B:1 W:1	
186	R:1	
187		
189	T:1	
190	W:1	
190	A:1	
192	F:1	
193	B:1	
193	G:3	
195	W:1	
. 196	0:1	
197	T:1	
198	0:1	
199	B:1	
200	AA:1	
201	G:1	
202	B:1	
203	G:1	-
204	P:1	
205	AA:1	
206	Y:1	
207	Y:1	
208	AA:1	
209	G:1	
	<del>*</del>	

	31
210	H:1
211	C:1
212	H:1
213	W:2
214	Y:1
215	AB:1
216	K:1
217	M:1
218	AD:1
219	A:1
220	AA:1
221	G:1
222	G:1
223	G:1; H:2; S:2; X:1
224	G:1
225	G:1
226	B:1
227	P:1
228	
229	G:1
230	T:1
231	T:1
232	K:1
233	S:1
234	O:1
235	F:1
236	
237	B:1
238	W:1
239	G:1
240	R:1
241	A:1
242	W:1
	P:1
243	H:1
245	D:1
245	C:1
247	
248	P:1
249	F:1
250	AB:1
251	W:1
252	H:1
253	B:1
254	S:1
255	T:1
256	W:1
257	T:1

259   P:1   260   W:1   261   H:1   262   K:1   263   K:1   264   C:1; E:1; F:1; I:4; L:1; N:22; O:1; P:1; S:1; T:9; AA:1   265   A:1   266   T:1   267   K:1   268   H:1   269   T:2   270   T:1   271   T:1   272   B:1   274   T:1   275   G:1   276   AA:1   277   T:1   278   AB:1   279   T:1   278   AB:1   279   T:1   280   W:1   281   F:1   282   K:1   283   H:1   284   O:1   285   W:1   284   O:1   285   W:1   286   B:2; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1   289   K:2; P:12; W:1; AC:2   289   K:2; P:8; W:1; C:2   290   B:1   292   B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1   295   H:1   296   AA:1   297   T:1   298   T:1   299   T:1   298   T:1   299   T:1   300   H:1; S:1   301   H:1   302   W:1   303   W:1   304   H:1   302   W:1   305   G:1   300   H:1; S:1   300   H:1; S:1   300   H:1; S:1   300   H:1   302   W:1   300   H:1   300   W:1   300   M:1   300   M	238	AA:2
261 H:1 262 K:1 263 K:1 264 C:1; E:1; F:1; I:4; L:1; N:22; O:1; F:1; S:1; T:9; AA:1 265 A:1 266 T:1 267 K:1 268 H:1 269 T:2 270 T:1 271 T:1 271 T:1 272 B:1 273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1; AC:2 290 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 297 T:1 298 T:1 299 T:1 299 T:1 299 T:1 299 T:1 299 T:1 290 H:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 299 T:1 300 H:1; S:1	259	P:1
262 K:1 263 K:1 264 C:1; E:1; F:1; I:4; L:1; N:22; O:1; P:1; S:1; T:9; AA:1 265 A:1 266 T:1 267 K:1 268 H:1 269 T:2 270 T:1 271 T:1 272 B:1 273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1; AC:2 290 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 290 B:11; C:2; E:1; H:7; K:1; N:3; C:2; S:5; T:1; U:1; V:2; Y:3; AA:1 291 H:1 292 B:10; C:2; C:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1 304 H:1	260	W:1
263 K:1 264 C:1; E:1; F:1; 1:4; L:1; N:22; O:1; P:1; S:1; T:9; AA:1 265 A:1 266 T:1 267 K:1 268 H:1 269 T:2 270 T:1 271 T:1 272 B:1 273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1; AC:2 290 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1	261	H:1
264 C.1; E.1; F.1; I.4; L.1; N.22; O.1; P.1; S.1; T.9; AA:1 265 A:1 266 T.1 268 H.1 269 T.2 270 T.1 271 T.1 271 B:1 272 B:1 273 Y:1 274 T.1 275 G:1 276 AA:1 277 T.1 278 AB:1 279 T.1 280 W:1 281 F.1 282 K.1 283 H.1 284 O:1 285 W:1 285 W:1 286 B:21; C.7; H.5; K.5; O.8; S.16; W.1; Y.3; Z.4; AA:2; AC:1 287 K.2; P.12; W:1; AC:2 288 S:1 289 K.2; P.8; W:1; AC:2 290 S:1 291 H:1 292 B:11; C.2; E:1; H.7; K.1; N.3; S:1; T.8; W:1; AA:28; AC:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 290 B:1 291 H:1 292 B:11; C.2; E:1; H.7; K.1; N.3; S:1; T.8; W:1; AA:28; AC:1 293 B:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1 304 H:1	262	K:1
265 A:1 266 T:1 267 K:1 268 H:1 269 T:2 270 T:1 271 T:1 272 B:1 273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1; AC:2 290 S:1 291 H:1 292 B:1; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1 304 H:1	263	K:1
265 A:1 266 T:1 267 K:1 268 H:1 269 T:2 270 T:1 271 T:1 272 B:1 273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1; AC:2 290 S:1 291 H:1 292 B:1; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1 304 H:1	264	C:1; E:1; F:1; I:4; L:1; N:22; O:1; P:1; S:1; T:9; AA:1
266 T:1 267 K:1 268 H:1 269 T:2 270 T:1 271 T:1 271 T:1 272 B:1 273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1; AC:2 290 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 W:1 302 W:1 303 W:1 304 H:1	265	
267 K:1 268 H:1 269 T:2 270 T:1 271 T:1 272 B:1 273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:12; W:1; AC:2 290 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1 304 H:1		T:1
268 H:1 269 T:2 270 T:1 271 T:1 272 B:1 273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1, AC:2 290 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 294 B:1 295 H:1 297 T:1 298 T:1 299 T:1 290 T:1 290 T:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1 304 H:1	267	K:1
269 T:2 270 T:1 271 T:1 271 T:1 272 B:1 273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1; AC:2 290 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1 304 H:1	268	H:1
271 T:1 272 B:1 273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 299 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1 304 H:1	269	T:2
272 B:1 273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1, AC:2 290 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1 304 H:1	270	T:1
273 Y:1 274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1, AC:2 290 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 304 H:1	271	T:1
274 T:1 275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1; AC:2 290 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1 304 H:1	272	B:1
275 G:1 276 AA:1 277 T:1 278 AB:1 279 T:1 280 W:1 281 F:1 282 K:1 283 H:1 284 O:1 285 W:1 286 B:21; C:7; H:5; K:5; O:8; S:16; W:1; Y:3; Z:4; AA:2; AC:1 287 K:2; P:12; W:1; AC:2 288 S:1 289 K:2; P:8; W:1; AC:2 290 S:1 291 H:1 292 B:11; C:2; E:1; H:7; K:1; N:3; S:1; T:8; W:1; AA:28; AC:1 293 B:6; C:3; G:1; H:6; K:4; N:4; O:3; Q:2; S:5; T:1; U:1; V:2; Y:3; AA:1 294 B:1 295 H:1 296 AA:1 297 T:1 298 T:1 299 T:1 300 H:1; S:1 301 H:1 302 W:1 303 W:1 304 H:1	273	Y:1
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378	AA:1
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419	F:1
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423	P:1
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505	G:2; H:1
506	W:1
507	B:1
508	W:1
509	AB:1
510	H:1
511	N:1
512	J:1
513	AA:1
514	T:2
515	AA:5
516	F:1
517	C:1; O:1
518	W:1
519	T:4
520	B:1
521	H:1
522	H:2; T:3
523	H:1
524	AA:1
525	W:1
526	C:2; E:1; J:1; R:3; S:4; AA:1
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528	S:1
529	P:1
530	B:1; H:1
531	0:1
532	Y:1
533	H:1
534	T:1
535	T:2
536	B:1
537	AD:1
538	AA:1
539	T:1
540	F:1
541	AD:1
542	W:1
543	W:1
544	F:1
545	T:1

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546	F:1
547	K:1
548	Y.1
549	S:1
550	B:1
551	B:1
552	B:1
553	H:1
554	P:1
555	G:1
556	H:1
557	K:1
558	B:1
559	R:1
560	AB:1
561	C:1; S:1; V:1
562	AA:1
563	K:1
564	P:1
565	K:1
566	G:1
567	W:1
568	E:1; W:2
569	W:1
570	B:2
571	0:1
572	T:1
573	B:1
574 575	T:1 B:1
<u>575</u>	B:3
577	B:1
578	V.1
579	H:1
580	AA:1
581	AA:1
582	AA:1
583	AA:1
584	AA:1
585	D:1
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587	H:1
588	AA:3
589	K:1
590	W:1
	K:1
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594	V:1
595	R:1
596	P:1
597	G:1; X:2; Z:1
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601	Y:1
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603	W:1
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609	F:1
610	K:1
611	M:1
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614	T:1
615	H:1
616	F:1
617	T:1
618	G:1
619	G:1
620	B:1
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622	W:1
623	T:1
624	AA:1
625	G:1
626	M:1
627	C:2; T:2; W:1; Y:1
628	T:1
629	J:1
630	T:1
631	P:1
632	H:1
633	H:1
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635	1:1
636	G:1
637	W:1
638	AA:1
639	W:1
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644	AA:1
645	T:1
646	K:1
647	F:1
648	F:1
649	F:1
650	T:1
651	W:1
652	T:1
653	T:1
654	P:1
655	B:1; H:2; N:1; T:3; Y:1
656	B:1
657	T:1
658	R:1
659	K:1
660	W:1
661	AA:1
662	Y:1
663	W:1
664	G:1
665	S:1
666	Y:1
667	F:1
668	T:1
669	B:1
670	F:1
671	T:1
672	A:2; B:6; C:1; G:1; H:3; J:1; L:1; P:2; Q:1; S:4; T:1; V:3; W:2; Y:1;
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673	T:1
674	G:1
675	F:1
676	M:1
677	G:1
678	Y:1
679	D:1
680	P:1
681	D:1
682	AA:1
683	G:1
684	K:1
685	G:1
686	P:1
687	B:3; C:2; D:2; E:2; J:4; V:2; AC:6

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688	AA:1
689	S:1
690	AA:1
691	H:1
692	AA:1
693	S:1
694	AB:1
695	T:1
696	H:1
697	B:4; E:1; F:1; P:1; T:2; Z:2
698	O:1
699	W:1
700	S:1
701	0:1
702	B;1
703	AB:1
704	H:1
705	B:1
706	H:1
707	G:1
708	F:1; H:1; K:1; W:2; AA:1
709	H:1
710	T:2
711	C:1
712	G:1
713	Y:1
714	C:1
715	Y:1
716	Z:1
717	P:1
718	G:1
719	S:1
720_	K:1
721	M:1
722	T:2
723	O:1; P:2; S:2
724	T:1
725	T:1
726	N:1
727	T:1
728	T:1
729	C:2; H:2; K:2; V:1; AC:1
730	B:7; H:2; Y:1
731	B:5; W:3
732	B:1; C:2; G:2; S:2; AA:9
733	B:6; C:2; G:1; H:10; O:2; P:6; Q:1; S:2; W:4; AC:2
734	B:6; O:1; V:1
735	C:1; O:2

736	B:1; H:2; N:1; T:3; Y:1
737	T:2
738	T:2
739	B:3; C:8; D:1; E:6; G:3; H:11; I:1; J:1; N:1; O:3; P:12; Q:3; S:2; T:2; W:1; AC:1; AD:8
740	H:2; Y:1
741	C:2; H:1
742	B:12; C:1; G:1; H:4; K:2; O:2; S:4; T:2; Y:2
743	AA:4
744	B:1; G:1; H:6; T:1; W:1
745	C:7; E:1; G:3; H:2; P:2; S:2; T:1; W:1; AD:2
746	G:2; S:1
747	T:2
748	S:3
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750	Y:1; AD:1
751	B:8; G:2; H:2; I:1; Q:2; S:2; T:1; W:2
752	T:3
753	P:4
754	B:1; H:2
755	B:7; C:1; G:6; H:2; K:1; U:2; V:1; Z:1
756	C:1; H:1; J:2; O:2; S:1; T:2; W:1; AA:1
757	B:1; C:1; K:3; S:1; V:1; Y:1
758	E:1; H:2; K:1; P:1; Q:1; AD:5
759	B:6; C:1; Y:1
760	B:4
761	W:2
762	B:3; C:7; H:9; N:1; S:1; T:1; Y:1; AA:1
763	N:1; S:1; AA:5
764	H:3
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766	H:2
767	C:1; AA:3
768	B:2; C:6; H:9; N:1; S:1; T:1; Y:1; AA:1
769	A:1; B:4; C:4; F:4; G:6; H:10; K:2; O:8; P:2; R:1; S:8; T:2; W:3; AA:2; AC:1
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771	AA:3
772	O:4
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774	P:2; X:4
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776	H:7
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778	B:6
779	B:3; C:1; G:1; H:2; K:1; Q:1; S:8; W:2; Y:9; AA:4
780	B:3; C:1; F:1; P:1; W:1; AC:1
781	I:2; N:1; P:1; R:3; AA:1
782	B:2

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783	H:1; P:2; S:3; AD:1
784	H:1; P:1; S:4; AD:1
785	T:2
786	D:1; AC:9
787	H:1; L:1; S:1
788	B:6; S:4
789	S:1; T:1
790	B:1; C:2; H:5; W:1; AD:1
791	B:3; C:2; D:3; E:2; J:4; V:3; AC:5
792	B:3; D:1; K:2; S:2; Y:1
793	B:2; G:2; AA:1
794	B:25; C:4; D:1; E:1; F:3; G:6; J:1; K:6; N:1; O:1; P:2; R:1; S:3; T:2;
-	W:2; X:1; Y:1; Z:1; AA:1; AC:2; AD:1
795	B:4; C:1; E:2; H:4; J:1; L:1; O:4; S:1; V:1; Y:3; Z:1
796	H:5
797	B:2; E:1; N:2
798	B:1; G:1; H:6; T:1; W:1
799	H:2
800	H:2; I:2; AA:1
801	A:2; B:4; C:14; D:1; H:2; K:1; N:2; S:4; T:1; W:2; AA:20
802	AA:17
803	B:2; G:3; H:3; S:1; U:1; AC:1; AD:2
804	C:1; S:2; T:2; X:2; AA:1; AC:1
805	B:5; C:6; D:5; H:17; J:2; K:4; N:1; O:6; P:2; S:5; T:5; W:1; X:1; Z:2;
806	AA:13; AC:3  B:2; C:3; D:3; H:6; J:2; K:1; N:1; O:3; P:1; S:2; T:4; W:1; X:1; Z:1; AA:5; AC:1
807	H:1; AC:4
808	R:13
809	B:3; W:4
810	B:16; S:1; Y:14
811	B:8; C:5; G:1; H:1; K:5; O:2; Q:2; R:2; S:2; T:3; Y:4; Z:2; AA:1; AC:1; AD:2
1600	T:4
1601	AA:3
1602	C:3; H:1
1603	H:2; AC:2
1604	B:7; C:1; E:1; H:1; P:2; R:3; S:2; T:2; Z:3; AA:2
1605	C:4; H:3; O:1
1606	A:3; B:13; C:14; D:2; E:10; F:3; G:19; H:32; K:11; O:5; P:2; R:3; S:16;
	T:4; W:2; Y:10; Z:8; AA:1; AC:3
1607	T:3
1608	B:3; P:2
1609	R:4
1610	B:4
1611	B:3; T:1
1612	T:2
1613	V:5
1614	D:3

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1615	AA:10	<u> </u>
1616	B:4	
1617	T:2	
1618	K:2; S:8; AA:1	
1619	B:2	1
1620	W:2	
1621	H:1; AB:1	
1622	H:2	

Table VI

Tissue code	Tissue type
Α	Bone Marrow
В	Brain
С	Cancerous prostate
D	Cerebellum
E	Colon
F	Dystrophic muscle
G	Fetal brain
Н	Fetal kidney
I	Fetal liver
J	Heart
K	Hypertrophic prostate
L	Kidney
M	Large intestine
N	Liver
0	Lung
P	Lymph ganglia
Q	Lymphocytes
R S T	Muscle
S	Prostate
	Ovary
U	Pancreas
V	Placenta
W	Spinal cord
X	Spleen
Y	Substantia nigra
Z	Surrenals
AA	Testis
AB	Thyroid
AC	Umbilical cord
AD	Uterus

In addition to categorizing the 5' ESTs and consensus contigated 5' ESTs with respect to their tissue of origin, the spatial and temporal expression patterns of the mRNAs corresponding to the 5' ESTs and consensus contigated 5' ESTs, as well as their expression levels, may be determined as described in Example 18 below.

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Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be discussed in more detail below.

Furthermore, 5' ESTs and consensus contigated 5' ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from the lack of expression, over expression, or under expression of a mRNA corresponding to a 5' EST or consensus contigated 5' EST. By comparing mRNA expression patterns and quantities in samples taken from healthy individuals with those from individuals suffering from a particular disease, 5' ESTs or consensus contigated 5' ESTs responsible for the disease may be identified.

It will be appreciated that the results of the above characterization procedures for 5' ESTs and consensus contigated 5' ESTs also apply to extended cDNAs (obtainable as described below) which contain sequences adjacent to the 5' ESTs and consensus contigated 5' ESTs. It will also be appreciated that if desired, characterization may be delayed until extended cDNAs have been obtained rather than characterizing the 5' ESTs or consensus contigated 5' ESTs themselves.

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#### **EXAMPLE 18**

# Evaluation of Expression Levels and Patterns of mRNAs Corresponding to EST-Related Nucleic Acids

Expression levels and patterns of mRNAs corresponding to EST-related nucleic acids may be 20 analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, an EST-related nucleic acid, fragment of an EST-related nucleic acid, positional segment of an EST-related nucleic acid, or fragment of a positional segment of an EST-related nucleic acid corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA polymerase promoter to produce 25 antisense RNA. Preferably, the EST-related nucleic acid, fragment of an EST-related nucleic acid, positional segment of an EST-related nucleic acid, or fragment of a positional segment of an EST-related nucleic acid is 100 or more nucleotides in length. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of 30 interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by 35 ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

The EST-related nucleic acid, fragment of an EST-related nucleic acid, positional segment of an EST-related nucleic acid, or fragment of a positional segment of an EST-related nucleic acid may also be

tagged with nucleotide sequences for the serial analysis of gene expression (SAGE) as disclosed in UK
Patent Application No. 2 305 241 A. In this method, cDNAs are prepared from a cell, tissue, organism
or other source of nucleic acid for which gene expression patterns must be determined. The resulting
cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first restriction

5 endonuclease, called an anchoring enzyme, having a recognition site which is likely to be present at least
once in most cDNAs. The fragments which contain the 5' or 3' most region of the cleaved cDNA are
isolated by binding to a capture medium such as streptavidin coated beads. A first oligonucleotide linker
having a first sequence for hybridization of an amplification primer and an internal restriction site for a
so called tagging endonuclease is ligated to the digested cDNAs in the first pool. Digestion with the
second endonuclease produces short tag fragments from the cDNAs.

A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internal restriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the tagging endonuclease to generate short tag fragments derived from the cDNAs in the second pool. The tags resulting from digestion of the first and second pools with the anchoring enzyme and the tagging endonuclease are ligated to one another to produce so called ditags. In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the EST-related nucleic acid, fragment of an EST-related nucleic acid, positional segment of an EST-related nucleic acid to determine which 5' ESTs, consensus contigated 5' ESTs, or extended cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5' ESTs, consensus contigated 5' ESTs, or extended cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

Quantitative analysis of gene expression may also be performed using arrays. As used herein,
the term array means a one dimensional, two dimensional, or multidimensional arrangement of ESTrelated nucleic acids, fragments of EST-related nucleic acids, positional segments EST-related nucleic
acids, or fragments of positional segments of EST-related nucleic acids. Preferably, the EST-related
nucleic acids, fragments of EST-related nucleic acids, positional segments EST-related nucleic acids, or
fragments of positional segments of EST-related nucleic acids are at least 10, 12, 15, 18, 20, 23, 25, 28,
30, 35, 40, or 50 nucleotides in length. More preferably, the EST-related nucleic acids, fragments of
EST-related nucleic acids, positional segments EST-related nucleic acids, or fragments of positional
segments of EST-related nucleic acids are at least 100 nucleotide long. More preferably, the fragments
are more than 100 nucleotides in length. In some embodiments, the EST-related nucleic acids,
fragments of EST-related nucleic acids, positional segments EST-related nucleic acids, or fragments of
positional segments of EST-related nucleic acids may be more than 500 nucleotides long.

For example, quantitative analysis of gene expression may be performed with EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments EST-related nucleic acids, or

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fragments of positional segments of EST-related nucleic acids in a complementary DNA microarray as described by Schena et al. (Science 270:467-470, 1995; Proc. Natl. Acad. Sci. U.S.A. 93:10614-10619, 1996). EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments ESTrelated nucleic acids, or fragments of positional segments of EST-related nucleic acids are amplified by 5 PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm<sup>2</sup> microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at 60°C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom 15 filter set. Accurate differential expression measurements are obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments EST-related nucleic acids, or fragments of positional segments of EST-related nucleic acids in complementary DNA arrays as 20 described by Pietu et al. (Genome Research 6:492-503, 1996). The EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments EST-related nucleic acids, or fragments of positional segments of EST-related nucleic acids thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides. After hybridization and washing in controlled conditions, the hybridized mRNAs are detected by phospho-25 imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

Alternatively, expression analysis of the EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments EST-related nucleic acids, or fragments of positional segments of EST-related nucleic acids can be done through high density nucleotide arrays as described by Lockhart 30 et al. (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky et al. (Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments EST-related nucleic acids, or fragments of positional segments of EST-related nucleic acids are synthesized directly on the chip (Lockhart et al., supra) or synthesized and then addressed to the chip (Sosnowsky et al., supra). 35 Preferably, the oligonucleotides are about 20 to 25 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are synthesized from the appropriate mRNA population and then randomly fragmented to an

average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart et al, supra and application of different electric fields (Sonowsky et al, supra.), the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target 5 oligonucleotide in different cDNA samples indicates a differential expression of the mRNA corresponding to the 5' EST, consensus contigated 5' EST or extended cDNA from which the oligonucleotide sequence has been designed.

# IV. Use of 5' ESTs to Clone Extended cDNAs and to Clone the Corresponding Genomic DNAs

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Once 5' ESTs or consensus contigated 5' ESTs which include the 5' end of the corresponding mRNAs have been selected using the procedures described above, they can be utilized to isolate extended cDNAs which contain sequences adjacent to the 5' ESTs or consensus contigated 5' ESTs. The extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site. If the extended cDNA encodes a 15 secreted protein, it may contain the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide.

Extended cDNAs which include the entire coding sequence of the protein encoded by the corresponding mRNA are referred to herein as "full-length cDNAs." Alternatively, the extended cDNAs may not include the entire coding sequence of the protein encoded by the corresponding mRNA, 20 although they do include sequences adjacent to the 5'ESTs or consensus contigated 5' ESTs. In some embodiments in which the extended cDNAs are derived from an mRNA encoding a secreted protein, the extended cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

Examples 19 and 20 below describe a general method for obtaining extended cDNAs using 5' 25 ESTs or consensus contigated 5' ESTs and nucleic acid homologous thereto. Example 21 below describes the cloning and sequencing of several extended cDNAs, including full-length cDNAs which include the authentic 5' end of the corresponding mRNA for several secreted proteins.

The methods of Examples 19 and 20 can also be used to obtain extended cDNAs which encode less than the entire coding sequence of proteins encoded by the genes corresponding to the 5' ESTs or 30 consensus contigated 5'ESTs. In some embodiments, the extended cDNAs isolated using these methods encode at least 5,10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of one of the proteins encoded by the sequences of SEQ ID NOs. 24-811 and 1600-1622. In some embodiments, the extended cDNAs isolated using these methods encode at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of one of the proteins encoded by the sequences of SEQ ID NOs. 24-

General Method for Using 5' ESTs or Consensus Contigated 5'ESTs to Clone and Sequence Extended cDNAs which Include the Entire Coding Region and the Authentic 5'End of the Corresponding mRNA

The following general method may be used to quickly and efficiently isolate extended cDNAs including sequence adjacent to the sequences of the 5' ESTs or Consensus Contigated 5'ESTs used to 5 obtain them. This method may be applied to obtain extended cDNAs for any 5' EST or consensus contigated 5' EST of the invention, including those 5' ESTs and consensus contigated 5' ESTs encoding secreted proteins. This method is illustrated in Figure 3.

## 1. Obtaining Extended cDNAs

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The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription 10 reaction is conducted on purified mRNA with a poly dT primer containing a nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. Such a primer and a commercially-available reverse transcriptase enzyme are added to a buffered mRNA sample yielding a reverse transcript anchored at the 3' polyA site of the RNAs. Nucleotide monomers are then added to complete the first strand synthesis.

After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the alkaline hydrolysis and the residual poly dT primer can be eliminated with an exclusion column.

Subsequently, a pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST or consensus contigated 5' EST and the known 3' end added by the poly dT primer 20 used in the first strand synthesis. Software used to design primers are either based on GC content and melting temperatures of oligonucleotides, such as OSP (Illier and Green, PCR Meth. Appl. 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais et al., Nucleic Acids Res. 19: 3887-3891, 1991) such as PC-Rare (http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html). Preferably, the nested primers at the 5' end and the nested primers at the 3' end 25 are separated from one another by four to nine bases. These primer sequences may be selected to have

A first PCR run is performed using the outer primer from each of the nested pairs. A second PCR run using the inner primer from each of the nested pairs is then performed on a small sample of the first PCR product. Thereafter, the primers and remaining nucleotide monomers are removed.

#### 30 2. Sequencing Extended cDNAs or Fragments Thereof

melting temperatures and specificities suitable for use in PCR.

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the entire coding sequence. Such an extended cDNA may be used in a direct cloning procedure as described 35 in section a below. However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. Such incomplete PCR products are submitted to a modified procedure described in section b below.

When the resulting nested PCR product contains the complete coding sequence, as predicted from the 5'EST or consensus contigated 5' EST sequence, it is directly cloned in an appropriate vector as described in section 3.

### 5 b) Nested PCR products containing incomplete ORFs

When the amplicon does not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products.

Once the full coding sequence has been completely determined, new primers compatible for PCR use are then designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, *i.e.* the polyA tract and sometimes the polyadenylation signal, as illustrated in Figure 3. Such extended cDNAs are then cloned into an appropriate vector as described in section 3.

### c) Sequencing extended cDNAs

Sequencing of extended cDNAs can be performed using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer.

In order to sequence long PCR fragments, primer walking is performed using software such as 20 OSP to choose primers and automated computer software such as ASMG (Sutton *et al.*, *Genome Science Technol.* 1: 9-19, 1995) to construct contigs of walking sequences including the initial 5' tag. Preferably, primer walking is performed until the sequences of full length cDNAs are obtained.

Completion of the sequencing of a given extended cDNA fragment may be assessed by comparing the sequence length to the size of the corresponding nested PCR product. When Northern blot data are available, the size of the mRNA detected for a given PCR product may also be used to finally assess that the sequence is complete. Sequences which do not fulfill these criteria are discarded and will undergo a new isolation procedure.

### 3. Cloning Extended cDNAs

The PCR product containing the full coding sequence is then cloned in an appropriate vector.

30 For example, the extended cDNAs can be cloned into any expression vector known in the art, such as pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA).

Cloned PCR products are then entirely sequenced in order to obtain at least two sequences per clone. Preferably, the sequences are obtained from both sense and antisense strands according to the aforementioned procedure with the following modifications. First, both 5' and 3' ends of cloned PCR products are sequenced in order to confirm the identity of the clone. Second, primer walking is performed if the full coding coding region has not been obtained yet. Contigation is then performed using primer walking sequences for cloned products as well as walking sequences that have already

contigated for uncloned PCR products. The sequence is considered complete when the resulting contigs include the whole coding region as well as overlapping sequences with vector DNA on both ends. All the contigated sequences for each cloned amplicon are then used to obtain a consensus sequence.

### 5 4. Selection of Cloned Full length Sequences

# a) Computer analysis of extended cDNAs

Following identification of contaminants and masking of repeats, structural features, e.g. polyA tail and polyadenylation signal, of the sequences of extended cDNAs are subsequently determined using methods known to those skilled in the art. For example, algorithm, parameters and 10 criteria defined in Figure 10 may be used. Briefly, a polyA tail is defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it. The polyA tail search is restricted to the last 20 nucleotides of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. To search for a polyadenylation signal, the polyA tail is clipped from the full-length sequence. The 50 nucleotides preceding the polyA tail 15 are searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors as well as known variation in the canonical sequence of the polyadenylation signal.

Functional features, e.g. ORFs and signal sequences, of the sequences of extended cDNAs are subsequently determined as follows. The 3 upper strand frames of extended cDNAs are searched for 20 ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 80 amino acids are preferred. If extended cDNAs encoding secreted proteins are desired, each found ORF is then scanned for the presence of a signal peptide using the matrix method described in Example 13.

Sequences of extended cDNAs are then compared, on a nucleotidic or proteic basis, to public 25 sequences available at the time of filing.

#### b) Selection of full-length cDNAs of interest

A negative selection may then be performed in order to eliminate unwanted cloned sequences resulting from either contaminants or PCR artifacts as follows. Sequences matching contaminant sequences such as vector DNA, tRNA, mtRNA, rRNA sequences are discarded as well as those 30 encoding ORF sequences exhibiting extensive homology to repeats. Sequences obtained by direct cloning (section 1a) but lacking polyA tail may be discarded. Only ORFs ending either before the polyA tail (section 1a) or before the end of the cloned 3'UTR (section 1b) may be selected. If extended cDNAs encoding secreted proteins are desired, ORFs containing a signal peptide are considered. In addition, ORFs containing unlikely mature proteins such as mature proteins which size is less than 20 amino acids 35 or less than 25% of the immature protein size may be eliminated.

Then, for each remaining full length cDNA containing several ORFs, a preselection of ORFs may be performed using the following criteria. The longest ORF is preferred. If extended cDNAs

encoding secreted proteins are desired and if the ORF sizes are similar, the chosen ORF is the one which signal peptide has the highest score according to Von Heijne method.

Sequences of full length cDNA clones may then be compared pairwise after masking of the repeat sequences. Full-length cDNA sequences exhibiting extensive homology may be clustered in the same class. Each cluster may then be subjected to a cluster analysis that detects sequences resulting from internal priming or from alternative splicing, identical sequences or sequences with several frameshifts. A selection may be operated between clones belonging to the same class in order to detect clones encoding homologous but distinct ORFs which may be both selected if they both contain sequences of interest.

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Selection of full-length cDNA clones encoding sequences of interest may subsequently be performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal) are first checked. Then, homologies with known nucleic acids and proteins are examined in order to determine whether the clone sequence match a known nucleotide/protein sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there is no extensive 15 match with sequences other than ESTs or genomic DNA, or if the clone sequence brings substantial new information, such as encoding a protein resulting from alternative splicing of an mRNA coding for an already known protein, the sequence is kept. Examples of such cloned full-length cDNAs containing sequences of interest are described in Example 21. Sequences resulting from chimera or double inserts or located on chromosome breaking points as assessed by homology to other sequences may be 20 discarded during this procedure.

Extended cDNAs prepared as described above may be subsequently engineered to obtain nucleic acids which include desired portions of the extended cDNA using conventional techniques such as subcloning, PCR, or in vitro oligonucleotide synthesis. For example, nucleic acids which include only the full coding sequences may be obtained using techniques known to those skilled in the art.

25 Alternatively, conventional techniques may be applied to obtain nucleic acids which contain only part of the coding sequences. In the case of nucleic acids encoding secreted proteins, nucleic acids containing only the coding sequence for the mature protein remaining after the signal peptide is cleaved off or nucleic acids which contain only the coding sequences for the signal peptides may be obtained.

Similarly, nucleic acids containing any other desired portion of the coding sequences for the 30 encoded protein may be obtained. For example, the nucleic acid may contain at least 10, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400 or 500 consecutive bases of an extended cDNA.

Once an extended cDNA has been obtained, it can be sequenced to determine the amino acid sequence it encodes. Once the encoded amino acid sequence has been determined, one can create and identify any of the many conceivable cDNAs that will encode that protein by simply using the 35 degeneracy of the genetic code. For example, allelic variants or other homologous nucleic acids can be identified as described below. Alternatively, nucleic acids encoding the desired amino acid sequence can be synthesized in vitro.

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In a preferred embodiment, the coding sequence may be selected using the known codon or codon pair preferences for the host organism in which the cDNA is to be expressed.

In addition to PCR based methods for obtaining cDNAs which include the authentic 5'end of the corresponding mRNA as well as the complete protein coding sequence of the corresponding mRNA, 5 traditional hybridization based methods may also be employed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the 5' ESTs or consensus contigated 5' ESTS were derived, mRNAs corresponding to the extended cDNAs, or nucleic acids which are homologous to extended cDNAs, 5' ESTs, or consensus contigated 5' ESTs. Example 19 below provides examples of such methods.

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#### **EXAMPLE 20**

Methods for Obtaining Extended cDNAs which Include the Entire Coding Region and the Authentic 5'End of the Corresponding mRNA or Nucleic Acids Homologous to Extended cDNAs, 5' ESTs or Consensus Contigated 5' ESTs

A full-length cDNA library can be made using the strategies described in Example 7. Alternatively, a cDNA library or genomic DNA library may be obtained from a commercial source or made using techniques familiar to those skilled in the art.

Such cDNA or genomic DNA libraries may be used to isolate extended cDNAs obtained from 5' ESTs or consensus contigated 5' ESTs or nucleic acids homologous to extended cDNAs, 5' ESTs, or 20 consensus contigated 5' ESTs as follows. The cDNA library or genomic DNA library is hybridized to a detectable probe. The detectable probe may comprise at least 10, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400 or 500 consecutive nucleotides of the 5' EST, consensus contigated 5' EST, or extended cDNA.

Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe 25 sequence are disclosed in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs. Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. The detectable probe described in the preceding paragraph is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Techniques for 30 labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, in vitro transcription, and non radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After blocking of non specific sites, the filter is incubated with the labeled probe for an amount of time sufficient to allow binding of the probe to cDNAs or genomic DNAs containing a sequence capable of hybridizing thereto.

By varying the stringency of the hybridization conditions used to identify cDNAs or genomic DNAs which hybridize to the detectable probe, cDNAs or genomic DNAs having different levels of homology to the probe can be identified and isolated as described below.

# 1. Identification of cDNA or Genomic DNA Sequences Having a High Degree of Homology to the Labeled Probe

To identify cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula: Tm=81.5+16.6(log (Na+))+0.41(fraction G+C)-(600/N) where N is the length of the probe.

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If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation Tm=81.5+16.6(log (Na+))+0.41(fraction G+C)-(0.63% formamide)-(600/N) where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100 µg denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100 µg denatured fragmented salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook *et al.*, *supra*.

Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where the probe comprises double stranded DNA, it is denatured before addition to the hybridization solution. The filter is contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to extended cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200 nucleotides in length, the hybridization may be carried out at 15-25°C below the Tm. For shorter probes, such as oligonucleotide probes, the hybridization may be conducted at 15-25°C below the Tm. Preferably, for hybridizations in 6X SSC, the hybridization is conducted at approximately 68°C. Preferably, for hybridizations in 50% formamide containing solutions, the hybridization is conducted at approximately 42°C.

All of the foregoing hybridizations would be considered to be under "stringent" conditions.

Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15 minutes. The filter is then washed with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour. Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

cDNAs or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

# 2. Obtaining cDNA or Genomic DNA Sequences Having Lower Degrees of Homology to the Labeled Probe

The above procedure may be modified to identify cDNAs or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain cDNAs or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a sodium concentration of approximately 1M. Following hybridization, the filter may be

washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below 25% formamide. cDNAs or genomic DNAs which have hybridized to the probe are identified by autoradiography.

3. Determination of the Degree of Homology between the Obtained cDNAs or Genomic DNAs and 5'ESTs, Consensus Contigated 5'ESTs, or Extended cDNAs or Between the Polypeptides Encoded by the Obtained cDNAs or Genomic DNAs and the Polypeptides Encoded by the 5'ESTs, Consensus Contigated 5'ESTs, or Extended cDNAs

To determine the level of homology between the hybridized cDNA or genomic DNA and the 5'EST, consensus contigated 5'EST or extended cDNA from which the probe was derived, the nucleotide sequences of the hybridized nucleic acid and the 5'EST, consensus contigated 5'EST or extended cDNA from which the probe was derived are compared. The sequences of the 5'EST, consensus contigated 5'EST or extended cDNA from which the probe was derived and the sequences of the cDNA or genomic DNA which hybridized to the detectable probe may be stored on a computer readable medium as described below and compared to one another using any of a variety of algorithms familiar to those skilled in the art, those described below.

To determine the level of homology between the polypeptide encoded by the hybridizing cDNA or genomic DNA and the polypeptide encoded by the 5'EST, consensus contigated 5'EST or extended cDNA from which the probe was derived, the polypeptide sequence encoded by the hybridized nucleic acid and the polypeptide sequence encoded by the 5'EST, consensus contigated 5'EST or extended cDNA from which the probe was derived are compared. The sequences of the polypeptide encoded by the 5'EST, consensus contigated 5'EST or extended cDNA from which the probe was derived and the polypeptide sequence encoded by the cDNA or genomic DNA which hybridized to the detectable probe may be stored on a computer readable medium as described below and compared to one another using any of a variety of algorithms familiar to those skilled in the art, those described below.

Protein and/or nucleic acid sequence homologies may be evaluated using any of the variety of sequence comparison algorithms and programs known in the art. Such algorithms and programs include, but are by no means limited to, TBLASTN, BLASTP, FASTA, TFASTA, and CLUSTALW (Pearson and Lipman, 1988, Proc. Natl. Acad. Sci. USA 85(8):2444-2448; Altschul et al., 1990, J. Mol. Biol. 215(3):403-410; Thompson et al., 1994, Nucleic Acids Res. 22(2):4673-4680; Higgins et al., 1996, Methods Enzymol. 266:383-402; Altschul et al., 1990, J. Mol. Biol. 215(3):403-410; Altschul et al., 1993, Nature Genetics 3:266-272).

In a particularly preferred embodiment, protein and nucleic acid sequence homologies are evaluated using the Basic Local Alignment Search Tool ("BLAST") which is well known in the art (see, e.g., Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. USA 87:2267-2268; Altschul et al., 1990, J. Mol. Biol. 215:403-410; Altschul et al., 1993, Nature Genetics 3:266-272; Altschul et al., 1997,

- 5 Nuc. Acids Res. 25:3389-3402). In particular, five specific BLAST programs are used to perform the following task:
  - (1) BLASTP and BLAST3 compare an amino acid query sequence against a protein sequence database;
- (2) BLASTN compares a nucleotide query sequence against a nucleotide sequence 10 database;
  - (3) BLASTX compares the six-frame conceptual translation products of a query nucleotide sequence (both strands) against a protein sequence database;
  - (4) TBLASTN compares a query protein sequence against a nucleotide sequence database translated in all six reading frames (both strands); and
- 15 (5) TBLASTX compares the six-frame translations of a nucleotide query sequence against the six-frame translations of a nucleotide sequence database.

The BLAST programs identify homologous sequences by identifying similar segments, which are referred to herein as "high-scoring segment pairs," between a query amino or nucleic acid sequence and a test sequence which is preferably obtained from a protein or nucleic acid sequence database. High-scoring segment pairs are preferably identified (i.e., aligned) by means of a scoring matrix, many of which are known in the art. Preferably, the scoring matrix used is the BLOSUM62 matrix (Gonnet et al., 1992, Science 256:1443-1445; Henikoff and Henikoff, 1993, Proteins 17:49-61). Less preferably, the PAM or PAM250 matrices may also be used (see, e.g., Schwartz and Dayhoff, eds., 1978, Matrices for Detecting Distance Relationships: Atlas of Protein Sequence and Structure, Washington: National Biomedical Research Foundation)

The BLAST programs evaluate the statistical significance of all high-scoring segment pairs identified, and preferably selects those segments which satisfy a user-specified threshold of significance, such as a user-specified percent homology. Preferably, the statistical significance of a high-scoring segment pair is evaluated using the statistical significance formula of Karlin (see, e.g., Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. USA 87:2267-2268).

The parameters used with the above algorithms may be adapted depending on the sequence length and degree of homology studied. In some embodiments, the parameters may be the default parameters used by the algorithms in the absence of instructions from the user.

In some embodiments, the level of homology between the hybridized nucleic acid and the extended cDNA, 5'EST, or 5' consensus contigated 5'EST from which the probe was derived may be determined using the FASTDB algorithm described in Brutlag *et al.* Comp. App. Biosci. 6:237-245, 1990. In such analyses the parameters may be selected as follows: Matrix=Unitary, k-tuple=4.

Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5. Gap Size Penalty=0.05, Window Size=500 or the length of the sequence which hybridizes to the probe, whichever is shorter. Because the FASTDB program does not consider 5' or 3' truncations when calculating homology levels, if the sequence which hybridizes to the probe is truncated relative to 5 the sequence of the extended cDNA, 5'EST, or consensus contigated 5'EST from which the probe was derived the homology level is manually adjusted by calculating the number of nucleotides of the extended cDNA, 5'EST, or consensus contigated 5' EST which are not matched or aligned with the hybridizing sequence, determining the percentage of total nucleotides of the hybridizing sequence which the non-matched or non-aligned nucleotides represent, and subtracting this percentage from the 10 homology level. For example, if the hybridizing sequence is 700 nucleotides in length and the extended cDNA, 5'EST, or consensus contigated 5' EST sequence is 1000 nucleotides in length wherein the first 300 bases at the 5' □end of the extended cDNA, 5'EST, or consensus contigated 5' EST are absent from the hybridizing sequence, and wherein the overlapping 700 nucleotides are identical, the homology level would be adjusted as follows. The non-matched, non-aligned 300 bases represent 30% of the length of 15 the extended cDNA, 5'EST, or consensus contigated 5' EST. If the overlapping 700 nucleotides are 100% identical, the adjusted homology level would be 100-30=70% homology. It should be noted that the preceding adjustments are only made when the non-matched or non-aligned nucleotides are at the 5'or 3'ends. No adjustments are made if the non-matched or non-aligned sequences are internal or under any other conditions.

For example, using the above methods, nucleic acids having at least 95% nucleic acid homology, at least 96% nucleic acid homology, at least 97% nucleic acid homology, at least 98% nucleic acid homology, at least 99% nucleic acid homology, or more than 99% nucleic acid homology to the extended cDNA, 5'EST, or consensus contigated 5' EST from which the probe was derived may be obtained and identified. Such nucleic acids may be allelic variants or related nucleic acids from other 25 species. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the extended cDNA, 5'EST, or consensus contigated 5' EST from which the probe was derived.

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Using the above methods and algorithms such as FASTA with parameters depending on the sequence length and degree of homology studied, for example the default parameters used by the 30 algorithms in the absence of instructions from the user, one can obtain nucleic acids encoding proteins having at least 99%, at least 98%, at least 97%, at least 96%, at least 95%, at least 90%, at least 85%, at least 80% or at least 75% homology to the protein encoded by the extended cDNA, 5'EST, or consensus contigated 5' EST from which the probe was derived. In some embodiments, the homology levels can be determined using the "default" opening penalty and the "default" gap penalty, and a scoring matrix 35 such as PAM 250 (a standard scoring matrix; see Dayhoff et al., in: Atlas of Protein Sequence and Structure, Vol. 5, Supp. 3 (1978)).

Alternatively, the level of polypeptide homology may be determined using the FASTDB algorithm described by Brutlag et al. Comp. App. Biosci. 6:237-245, 1990. In such analyses the parameters may be selected as follows: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=Sequence Length, Gap 5 Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the homologous sequence, whichever is shorter. If the homologous amino acid sequence is shorter than the amino acid sequence encoded by the extended cDNA, 5'EST, or consensus contigated 5' EST as a result of an N terminal and/or C terminal deletion the results may be manually corrected as follows. First, the number of amino acid residues of the amino acid sequence encoded by the extended cDNA, 5'EST, or consensus 10 contigated 5' EST which are not matched or aligned with the homologous sequence is determined. Then, the percentage of the length of the sequence encoded by the extended cDNA, 5'EST, or consensus contigated 5' EST which the non-matched or non-aligned amino acids represent is calculated. This percentage is subtracted from the homology level. For example wherein the amino acid sequence encoded by the extended cDNA, 5'EST, or consensus contigated 5' EST is 100 amino acids in length 15 and the length of the homologous sequence is 80 amino acids and wherein the amino acid sequence encoded by the extended cDNA or 5'EST is truncated at the N terminal end with respect to the homologous sequence, the homology level is calculated as follows. In the preceding scenario there are 20 non-matched, non-aligned amino acids in the sequence encoded by the extended cDNA, 5'EST, or consensus contigated 5' EST. This represents 20% of the length of the amino acid sequence encoded by 20 the extended cDNA, 5'EST, or consensus contigated 5' EST. If the remaining amino acids are 1005 identical between the two sequences, the homology level would be 100%-20%=80% homology. No adjustments are made if the non-matched or non-aligned sequences are internal or under any other conditions.

In addition to the above described methods, other protocols are available to obtain extended cDNAs using 5' ESTs or consensus contigated 5'ESTs as outlined in the following paragraphs.

Extended cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing polyA selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the polyA tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of SEQ ID NOs 24-811 and 1600-1622. Preferably, the primer comprises at least 10, 12, 15, 17, 18, 20, 23, 25, or 28 consecutive nucleotides from the sequences of SEQ ID NOs 24-811 and 1600-1622. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of SEQ ID NOs 24-811 and 1600-1622. If it is desired to obtain extended cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is

extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RT-PCR may be performed as described above using primers from both ends of the cDNA to be obtained.

Extended cDNAs containing 5' fragments of the mRNA may be prepared by hybridizing an mRNA comprising the sequences of SEQ ID NOs. 24-811 and 1600-1622 with a primer comprising a 5 complementary to a fragment of an EST-related nucleic acid hybridizing the primer to the mRNAs, and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least 10, 12, 15, 17, 18, 20, 23, 25, or 28 consecutive nucleotides of the sequences complementary to SEQ ID NOs. 24-811 and 1600-1622.

Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The 10 second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded extended cDNAs made using the methods described above are isolated and cloned. The extended cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, 15 avian, or insect cell.

Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described in Current Protocols in Molecular Biology, John 20 Wiley & Sons, Inc. 1997 and Sambrook et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989.

Alternatively, other procedures may be used for obtaining full-length cDNAs or extended cDNAs. In one approach, full-length or extended cDNAs are prepared from mRNA and cloned into double stranded phagemids as follows. The cDNA library in the double stranded phagemids is then 25 rendered single stranded by treatment with an endonuclease, such as the Gene II product of the phage F1 and an exonuclease (Chang et al., Gene 127:95-8, 1993). A biotinylated oligonucleotide comprising the sequence of a fragment of an EST-related nucleic acid is hybridized to the single stranded phagemids. Preferably, the fragment comprises at least 10, 12, 15, 17, 18, 20, 23, 25, or 28 consecutive nucleotides of the sequences of SEQ ID NOs. 24-811 and 1600-1622.

Hybrids between the biotinylated oligonucleotide and phagemids are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a magnet (Fry et al., Biotechniques, 13: 124-131, 1992). Thereafter, the resulting phagemids are released from the beads and converted into double stranded DNA using a primer specific for the 5' EST or consensus contigated 5'EST sequence used to design the biotinylated oligonucleotide. Alternatively, protocols such as the 35 Gene Trapper kit (Gibco BRL) may be used. The resulting double stranded DNA is transformed into bacteria. Extended cDNAs or full length cDNAs containing the 5' EST or consensus contigated 5'EST sequence are identified by colony PCR or colony hybridization.

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Using any of the above described methods in section III, a plurality of extended cDNAs containing full-length protein coding sequences or portions of the protein coding sequences may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

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### **EXAMPLE 21**

## Full Length cDNAs

The procedures described in Example 19 and 20 were used to obtain extended cDNAs or full length cDNAs derived from 5' ESTs in a variety of tissues. The following list provides a few examples of cDNAs obtained by these means.

Using this procedure, the full length cDNA of SEQ ID NO:1 (internal identification number 58-34-2-E7-FL2) was obtained. This cDNA encodes the signal peptide MWWFQQGLSFLPSALVIWTSA (SEQ ID NO:2) having a von Heijne score of 5.5.

Using this approach, the full length cDNA of SEQ ID NO:3 (internal identification number 48-15-19-3-G1-FL1) was obtained. This cDNA encodes the signal peptide MKKVLLLITAILAVAVG (SEQ ID NO: 4) having a von Heijne score of 8.2.

The full length cDNA of SEQ ID NO:5 (internal identification number 58-35-2-F10-FL2) was also obtained using this procedure. This cDNA encodes a signal peptide LWLLFFLVTAIHA (SEQ ID NO:6) having a von Heijne score of 10.7.

Furthermore, the polypeptides encoded by the extended or full-length cDNAs may be screened for the presence of known structural or functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the members of a protein family. The results obtained for the polypeptides encoded by a few full-length cDNAs derived from 5'ESTs that were screened for the presence of known protein signatures and motifs using the Proscan software from the GCG package and the Prosite 15.0 database are provided below.

The protein of SEQ ID NO: 8 encoded by the full-length cDNA SEQ ID NO: 7 (internal designation 78-8-3-E6-CL0\_1C) and expressed in adult prostate belong to the phosphatidylethanolamine-binding protein from which it exhibits the characteristic PROSITE signature from positions 90 to 112. Proteins from this widespread family, from nematodes to fly, yeast, rodent and primate species, bind hydrophobic ligands such as phospholipids and nucleotides. They are mostly expressed in brain and in testis and are thought to play a role in cell growth and/or maturation, in regulation of the sperm maturation, motility and in membrane remodeling. They may act either through signal transduction or through oxidoreduction reactions (for a review see Schoentgen and Jollès, *FEBS Letters*, 369:22-26 (1995)). Taken together, these data suggest that the protein of SEQ ID NO: 8 may play a role in cell growth, maturation and in membrane remodeling and/or may be related to male fertility. Thus, these protein may be useful in diagnosing and/or treating cancer, neurodegenerative diseases, and/or disorders related to male fertility and sterility.

The protein of SEQ ID No. 10 encoded by the full-length cDNA SEQ ID No. 9 (internal designation 108-013-5-O-H9-FLC) shows homologies with a family of lysophospholipases conserved among eukaryotes (yeast, rabbit, rodents and human). In addition, some members of this family exhibit a calcium-independent phospholipase A2 activity (Portilla et al, J. Am. Soc. Nephro., 9:1178-1186 (1998)). All members of this family exhibit the active site consensus GXSXG motif of carboxylesterases that is also found in the protein of SEQ ID No. 10 (position 54 to 58). In addition, this protein may be a membrane protein with one transmembrane domain as predicted by the software TopPred II (Claros and von Heijne, CABIOS applic. Notes, 10:685-686 (1994)). Taken together, these data suggest that the protein of SEQ ID NO:10 may play a role in fatty acid metabolism, probably as a phospholipase. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, cancer, diabetes, and neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. It may also be useful in modulating inflammatory responses to infectious agents and/or to suppress graft rejection.

The protein of SEQ ID NO: 12 encoded by the full-length cDNA SEQ ID NO: 11 (internal 15 designation 108-004-5-0-D10-FLC) shows remote homology to a subfamily of beta4galactosyltransferases widely conserved in animals (human, rodents, cow and chicken). Such enzymes, usually type II membrane proteins located in the endoplasmic reticulum or in the Golgi apparatus, catalyzes the biosynthesis of glycoproteins, glycolipid glycans and lactose. Their characteristic features defined as those of subfamily A in Breton et al, J. Biochem., 123:1000-1009 20 (1998) are pretty well conserved in the protein of SEQ ID NO: 12, especially the region I containing the DVD motif (positions 163-165) thought to be involved either in UDP binding or in the catalytic process itself. In addition, the protein of SEQ ID NO: 12 has the typical structure of a type II protein. Indeed, it contains a short 28-amino-acid-long N-terminal tail, a transmembrane segment from positions 29 to 49 and a large 278-amino-acid-long C-terminal tail as predicted by the software 25 TopPred II (Claros and von Heijne, CABIOS applic. Notes, 10:685-686 (1994)). Taken together, these data suggest that the protein of SEQ ID NO: 12 may play a role in the biosynthesis of polysaccharides, and of the carbohydrate moieties of glycoproteins and glycolipids and/or in cell-cell recognition. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, atherosclerosis, cardiovascular disorders, autoimmune disorders 30 and rheumatic diseases including rheumatoid arthritis.

The protein of SEQ ID NO: 14 encoded by the full-length cDNA SEQ ID NO: 13 (internal designation 108-009-5-0-A2-FLC) shows extensive homology to the bZIP family of transcription factors, and especially to the human luman protein (Lu et al., Mol. Cell. Biol., 17:5117-5126 (1997))). The match include the whole bZIP domain composed of a basic DNA-binding domain and of a leucine zipper allowing protein dimerization. The basic domain is conserved in the protein of SEQ ID NO: 14 as shown by the characteristic PROSITE signature (positions 224-237) except for a conservative substitution of a glutamic acid with an aspartic acid in position 233. The typical

PROSITE signature for leucine zipper is also present (positions 259 to 280). Taken together, these data suggest that the protein of SEQ ID NO: 14 may bind to DNA, hence regulating gene expression as a transcription factor. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer.

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Bacterial clones containing plasmids containing the full length cDNAs described above are presently stored in the inventor's laboratories under the internal identification numbers provided above. The inserts may be recovered from the deposited materials by growing an aliquot of the appropriate bacterial clone in the appropriate medium. The plasmid DNA can then be isolated using plasmid isolation procedures familiar to those skilled in the art such as alkaline lysis minipreps or large scale 10 alkaline lysis plasmid isolation procedures. If desired the plasmid DNA may be further enriched by centrifugation on a cesium chloride gradient, size exclusion chromatography, or anion exchange chromatography. The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the insertion. The PCR product which corresponds to the cDNA insert 15 can then be manipulated using standard cloning techniques familiar to those skilled in the art.

# V. Expression of Proteins or Polypeptides Encoded by EST-related nucleic acids or Fragments thereof

EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-20 related nucleic acids, and fragments of positional segments of EST-related nucleic acids may be used to express the polypeptides which they encode. In particular, they may be used to express EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides, or fragments of positional segments of EST-related polypeptides. In some embodiments, the ESTrelated nucleic acids, positional segments of EST-related nucleic acids, and fragments of positional 25 segments of EST-related nucleic acids may be used to express the full polypeptide (i.e. the signal peptide and the mature polypeptide) of a secreted protein, the mature protein (i.e. the polypeptide generated after cleavage of the signal peptide), or the signal peptide of a secreted protein. If desired, nucleic acids encoding the signal peptide may be used to facilitate secretion of the expressed protein. It will be appreciated that a plurality of EST-related nucleic acids, fragments of EST-related nucleic acids, 30 positional segments of EST-related nucleic acids, or fragments of positional segments of EST-related nucleic acids may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

## **EXAMPLE 22**

To express their encoded proteins, the EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids, or fragments of positional segments of EST-related nucleic acids are cloned into a suitable expression vector. In some instances, nucleic acids encoding EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides or fragments of positional segments of EST-related polypeptides may be cloned into a suitable expression vector.

In some embodiments, the nucleic acids inserted into the expression vector may comprise the coding sequence of a sequence selected from the group consisting of SEQ ID NOs. 24-811. In other embodiments, the nucleic acids inserted into the expression vector may comprise may comprise the full coding sequence (i.e. the nucleotides encoding the signal peptide and the mature polypeptide) of one of SEQ ID Nos. 766-792. In some embodiments, the nucleic acid inserted into the expression vector may comprise the nucleotides of one of the sequences of SEQ ID Nos. 766-792 which encode the mature polypeptide (i.e. the nucleotides encoding the polypeptide generated after cleavage of the signal peptide). In further embodiments, the nucleic acids inserted into the expression vector may comprise the nucleotides of 24-728 and 766-792 which encode the signal peptide to facilitate secretion of the expressed protein. The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

The nucleic acid inserted into the expression vector may encode a polypeptide comprising the one of the sequences of SEQ ID Nos. 812-1599. In some embodiments, the nucleic acid inserted into the expression vector may encode the full polypeptide sequence (i.e. the signal peptide and the mature polypeptide) included in one of SEQ ID Nos. 1554-1580. In other embodiments, the nucleic acid inserted into the expression vector may encode the mature polypeptide (i.e. the polypeptide generated after cleavage of the signal peptide) included in one of the sequences of SEQ ID Nos. 1554-1580. In further embodiments, the nucleic acids inserted into the expression vector may encode the signal peptide included in one of the sequences of 812-1516 and 1554-1580.

The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, *et al.*, U.S. Patent No. 5,082,767.

The following is provided as one exemplary method to express the proteins encoded by the nucleic acids described above. In some instances the nucleic acid encoding the protein or polypeptide to

be expressed includes a methionine initiation codon and a polyA signal. If the nucleic acid encoding the polypeptide to be expressed lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the nucleic acid encoding the protein or polypeptide to be expressed lacks a polyA signal, this sequence can 5 be added to the construct by, for example, splicing out the polyA signal from pSG5 (Stratagene) using BglI and SalI restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex thymidine kinase promoter and the selectable neomycin gene. 10 The nucleic acid encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the nucleic acid encoding the protein or polypeptide to be expressed and containing restriction endonuclease sequences for Pst I incorporated into the 5'primer and Bglll at the 5' end of 3' primer, taking care to ensure that the nucleic acid encoding the protein or polypeptide to be expressed is correctly positioned with respect to the poly A signal. The purified 15 fragment obtained from the resulting PCR reaction is digested with PstI, blunt ended with an exonuclease, digested with Bgl II, purified and ligated to pXT1, now containing a poly A signal and digested with BglII.

The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification.

20 Positive transfectants are selected after growing the transfected cells in 600 µg/ml G418 (Sigma, St. Louis, Missouri).

Alternatively, the nucleic acid encoding the protein or polypeptide to be expressed may be cloned into pED6dpc2. The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as COS 1 cells. Methotrexate resistant cells are selected and expanded. The expressed protein or polypeptide may be isolated, purified, or enriched as described above.

To confirm expression of the desired protein or polypeptide, the proteins or polypeptides produced by cells containing a vector with a nucleic acid insert encoding the protein or polypeptide are compared to those lacking such an insert. The expressed proteins are detected using techniques familiar to those skilled in the art such as Coomassie blue or silver staining or using antibodies against the protein or polypeptide encoded by the nucleic acid insert. Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate nucleic acid. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the nucleic acid.

If the proteins or polypeptides encoded by the nucleic acid inserts are secreted, medium

35 prepared from the host cells or organisms containing an expression vector which contains a nucleic acid insert encoding the desired protein or polypeptide is compared to medium prepared from the control cells or organism. The presence of a band in medium from the cells containing the nucleic acid insert which

is absent from preparations from the control cells indicates that the protein or polypeptide encoded by the nucleic acid insert is being expressed and secreted. Generally, the band corresponding to the protein encoded by the nucleic acid insert will have a mobility near that expected based on the number of amino acids in the open reading frame of the nucleic acid insert. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector with an insert encoding a secreted protein or portion thereof can be compared to the proteins expressed in control host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector with an insert which is absent in samples from cells containing the expression vector without an insert indicates that the desired protein or portion thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or portion thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

The expressed protein or polypeptide may be purified, isolated or enriched using a variety of methods. In some methods, the protein or polypeptide may be secreted into the culture medium via a native signal peptide or a heterologous signal peptide operably linked thereto. In some methods, the protein or polypeptide may be linked to a heterologous polypeptide which facilitates its isolation, purification, or enrichment such as a nickel binding polypeptide. The protein or polypeptide may also be obtained by gel electrophoresis, ion exchange chromatography, size chromatography, hplc, salt precipitation, immunoprecipitation, a combination of any of the preceding methods, or any of the isolation, purification, or enrichment techniques familiar to those skilled in the art.

The protein encoded by the nucleic acid insert may also be purified using standard

25 immunochromatography techniques using immunoaffinity chromatography with antibodies directed against the encoded protein or polypeptide as described in more detail below. If antibody production is not possible, the nucleic acid insert encoding the desired protein or polypeptide may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies, the coding sequence of the nucleic acid insert is ligated in frame with the gene encoding the other half of the chimera. The other half of the chimera may be β-globin or a nickel binding polypeptide. A chromatography matrix having antibody to β-globin or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites may be engineered between the β-globin gene or the nickel binding polypeptide and the extended cDNA or portion thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

One useful expression vector for generating  $\beta$ -globin chimerics is pSG5 (Stratagene), which encodes rabbit  $\beta$ -globin. Intron II of the rabbit  $\beta$ -globin gene facilitates splicing of the expressed transcript, and the polyadenylation signal incorporated into the construct increases the level of

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expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis et al., (Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro Express<sup>TM</sup> Translation Kit (Stratagene).

Following expression and purification of the proteins or polypeptides encoded by the nucleic acid inserts, the purified proteins may be tested for the ability to bind to the surface of various cell types as described in Example 23 below. It will be appreciated that a plurality of proteins expressed from these nucleic acid inserts may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described below, as well as other biological roles for which assays for determining activity are available.

#### **EXAMPLE 23**

Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface

The EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids, fragments of positional segments of EST-related nucleic acids, nucleic acids encoding the EST-related polypeptides, nucleic acids encoding fragments of the EST-related polypeptides, nucleic acids encoding fragments of positional segments of EST-related polypeptides, or nucleic acids encoding fragments of positional segments of EST-related polypeptides are cloned into expression vectors such as those described in Example 22. The encoded proteins or polypeptides are purified, isolated, or enriched as described above. Following purification, isolation, or enrichment, the proteins or polypeptides are labeled using techniques known to those skilled in the art. The labeled proteins or polypeptides are incubated with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are

washed to remove non-specifically bound proteins or polypeptides. The specifically bound labeled proteins or polypeptides are detected by autoradiography. Alternatively, unlabeled proteins or polypeptides may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent molecule, attached thereto.

Specificity of cell surface binding may be analyzed by conducting a competition analysis in
which various amounts of unlabeled protein or polypeptide are incubated along with the labeled protein or polypeptide. The amount of labeled protein or polypeptide bound to the cell surface decreases as the amount of competitive unlabeled protein or polypeptide increases. As a control, various amounts of an unlabeled protein or polypeptide unrelated to the labeled protein or polypeptide is included in some binding reactions. The amount of labeled protein or polypeptide bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled protein, indicating that the protein or polypeptide encoded by the nucleic acid binds specifically to the cell surface.

As discussed above, human proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The human proteins or polypeptides made as described above may be evaluated to determine their physiological activities as described below.

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#### **EXAMPLE 24**

# Assaying the Expressed Proteins or Polypeptides for Cytokine, Cell Proliferation or Cell Differentiation Activity

As discussed above, some human proteins act as cytokines or may affect cellular proliferation or 10 differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein or polypeptide of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M<sup>+</sup> (preB 15 M<sup>-</sup>), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins or polypeptides prepared as described above may be evaluated for their ability to regulate T cell or thymocyte proliferation in assays such as those described above or in the following references: Current Protocols in Immunology, Ed. by J.E. Coligan et al., Greene Publishing Associates and Wiley-Interscience; Takai et al. J. Immunol. 137:3494-3500, 1986., Bertagnolli et al. J. Immunol. 145:1706-1712, 1990.,

20 Bertagnolli et al., Cellular Immunology 133:327-341, 1991. Bertagnolli, et al. J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells and thymocytes are known. These include the techniques disclosed in Current Protocols in Immunology. J.E. Coligan et al. Eds., 1:3.12.1-3.12.14, John Wiley and Sons, Toronto. 25 1994; and Schreiber, R.D. In Current Protocols in Immunology., supra 1: 6.8.1-6.8.8.

The proteins or polypeptides prepared as described above may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the art, including the assays in the following references: Bottomly et al., In Current Protocols in Immunology., supra. 1: 6.3.1-6.3.12,; deVries et al., J. Exp. 30 Med. 173:1205-1211, 1991; Moreau et al., Nature 36:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Nordan, R., In Current Protocols in Immunology., supra. 1: 6.6.1-6.6.5; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Bennett et al in Current Protocols in Immunology supra 1: 6.15.1; Ciarletta et al In Current Protocols in Immunology. supra 1: 6.13.1.

35 The proteins or polypeptides prepared as described above may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (In vitro Assays for Mouse

Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in Current Protocols in Immunology supra; Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

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Those proteins or polypeptides which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is beneficial. Alternatively, as described in more detail below, nucleic acids encoding these proteins or polypeptides or nucleic acids regulating the expression of these proteins or polypeptides may be introduced into appropriate host cells to increase or decrease the 10 expression of the proteins or polypeptides as desired.

#### **EXAMPLE 25**

# Assaying the Expressed Proteins or Polypeptides

## for Activity as Immune System Regulators

The proteins or polypeptides prepared as described above may also be evaluated for their effects 15 as immune regulators. For example, the proteins or polypeptides may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (In vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in Current 20 Protocols in Immunology, J.E. Coligan et al. Eds, Greene Publishing Associates and Wiley-Interscience; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bowman et al., J. Virology 61:1992-1998; Bertagnolli et al. Cell. Immunol. 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 25 1994.

The proteins or polypeptides prepared as described above may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, J. Immunol. 144:3028-3033, 1990; Mond et al. in Current Protocols in Immunology, 1: 30 3.8.1-3.8.16, supra.

The proteins or polypeptides prepared as described above may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (In vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 35 7 (Immunologic Studies in Humans) in Current Protocols in Immunology, supra; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

The proteins or polypeptides prepared as described above may also be evaluated for their effect on dendritic cell mediated activation of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., J. Exp. Med. 173:549-559, 1991; Macatonia et al., J. 5 Immunol. 154:5071-5079, 1995; Porgador et al J. Exp. Med 182:255-260, 1995; Nair et al., J. Virol. 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al J. Exp. Med 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., J. Exp. Med 172:631-640, 1990.

The proteins or polypeptides prepared as described above may also be evaluated for their 10 influence on the lifetime of lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Res. 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, J. Immunol. 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., Int. J. Oncol. 1:639-648, 1992.

The proteins or polypeptides prepared as described above may also be evaluated for their influence on early steps of T-cell commitment and development. Numerous assays for such activity are familiar to those skilled in the art, including without limitation the assays disclosed in the following references: Antica et al., Blood 84:111-117, 1994; Fine et al., Cell. Immunol. 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

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Those proteins or polypeptides which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. For example, the protein or polypeptide may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the 25 cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using the protein or polypeptide including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., plamodium. and various fungal infections such as 30 candidiasis. Of course, in this regard, a protein or polypeptide may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Alternatively, the proteins or polypeptides prepared as described above may be used in treatment of autoimmune disorders including, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-35 Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graftversus-host disease and autoimmune inflammatory eye disease. Such a protein or polypeptide may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic

asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using the protein or polypeptide.

Using the proteins or polypeptides of the invention it may also be possible to regulate immune responses either up or down. Down regulation may involve inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active non-antigen-specific process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after the end of exposure to the tolerizing agent.

Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions, such as, for example, B7 costimulation), e.g., preventing high level 15 lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks 20 interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody). prior to transplantation, can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen 25 function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigenblocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the 30 function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed.,

Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against 5 self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor/ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which potentially involved in the disease 10 process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmuno 15 collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may involve either enhancing an existing immune response or eliciting an initial immune response as shown 20 by the following examples. For instance, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory form of B lymphocyte antigens systemically.

Alternatively, antiviral immune responses may be enhanced in an infected patient by removing 25 T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing the proteins or polypeptides described above or together with a stimulatory form of the protein or polypeptide and reintroducing the in vitro primed T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells in vivo, thereby activating the T cells.

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In another application, upregulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Turnor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with one of the above-described nucleic acids encoding a protein or polypeptide can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express 35 a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor

cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the protein or polypeptide encoded by the nucleic acids described above having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary 5 costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules can be transfected with nucleic acids encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain and β2 microglobulin or an MHC class II a chain and an MHC class II b chain to thereby express MHC class I or MHC class II proteins 10 on the cell surface, respectively. Expression of the appropriate MHC class I or class II molecules in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a nucleic acid encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a protein or polypeptide having the 15 activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject. Alternatively, as described in more detail below, nucleic acids encoding these immune system regulator proteins or polypeptides or nucleic acids regulating the expression of such proteins or polypeptides may be introduced into 20 appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 26**

# Assaying the Expressed Proteins or Polypeptides for Hematopoiesis Regulating Activity

The proteins or polypeptides encoded by the nucleic acids described above may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins or polypeptides on embryonic stem cell differentiation may be evaluated. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson et al. Cell. Biol. 15:141-151, 1995; Keller et al., Mol. Cell. Biol. 13:473-486, 1993;

McClanahan et al., Blood 81:2903-2915, 1993.

The proteins or polypeptides encoded by the nucleic acids described above may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. Methylcellulose Colony Forming Assays, in <u>Culture of Hematopoietic Cells</u>.

35 R.I. Freshney, et al. Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. Primitive Hematopoietic

Colony Forming Cells with High Proliferative Potential, in Culture of Hematopoietic Cells. supra;

Neben et al., Experimental Hematology 22:353-359, 1994; Ploemacher, R.E. Cobblestone Area Forming Cell Assay, In <u>Culture of Hematopoietic Cells</u>. supra; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in <u>Culture of Hematopoietic Cells</u> supra; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in <u>Culture of Hematopoietic Cells</u>. supra.

5 Those proteins or polypeptides which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoeisis is beneficial. For example, a protein or polypeptide of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates 10 involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for 15 example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the abovementioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantion, including, without limitation, aplastic anemia and paroxysmal noctumal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as 25 normal cells or genetically manipulated for gene therapy. Alternatively, as described in more detail below, nucleic acids encoding these proteins or polypeptides or nucleic acids regulating the expression of these proteins or polypeptides may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

EXAMPLE 27

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# Assaying the Expressed Proteins or Polypeptides for Regulation of Tissue Growth

The proteins or polypeptides encoded by the nucleic acids described above may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. WO95/16035, International Patent Publication No. WO95/05846 and International Patent Publication No. WO91/07491.

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins or polypeptides which are involved in the regulation of tissue growth may then

5 be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue
growth is beneficial. For example, a protein or polypeptide may have utility in compositions used for
bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound
healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein or polypeptide encoded by the nucleic acids described above which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein or polypeptide of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone synthesis induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein or polypeptide of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the proteins or polypeptides encoded by the nucleic acids described above is tendon/ligament formation. A protein or polypeptide encoded by the nucleic acids described above, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a protein or polypeptide of the present invention contributes to the repair of tendon or ligaments defects of congenital, traumatic or other origin and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The proteins or polypeptides of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The proteins or polypeptides of the

invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The therapeutic compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The proteins or polypeptides of the present invention may also be useful for proliferation of 5 neural cells and for regeneration of nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein or polypeptide may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as 10 Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein or polypeptide of the invention.

Proteins or polypeptides of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein or polypeptide of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, 20 intestine, kidney, skin, endothelium) muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein or polypeptide of the invention may also exhibit angiogenic activity.

A protein or polypeptide of the present invention may also be useful for gut protection or 25 regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein or polypeptide of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, nucleic acids encoding tissue growth regulating activity proteins or polypeptides or nucleic acids regulating the expression of such proteins or polypeptides may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

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The proteins or polypeptides of the present invention may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale et al., Endocrinol: 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 5 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986. Chapter 6.12 in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Intersciece; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al. Eur. J. Immunol. 25:1744-1748; Gruber et al. J. Immunol. 152:5860-5867, 1994; Johnston et al., J Immunol. 153:1762-1768, 1994.

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Those proteins or polypeptides which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones are beneficial. For example, a protein or polypeptide may exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the 15 release of FSH. Thus, a protein or polypeptide of the present invention, alone or in heterodimers with a member of the inhibin family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein or polypeptide of the invention, as a homodimer or as a heterodimer with other protein subunits 20 of the inhibin-B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein or polypeptide of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, nucleic acids encoding reproductive hormone regulating activity proteins or polypeptides or nucleic acids regulating the expression of such proteins or polypeptides may be introduced into appropriate host cells to increase or decrease the expression of the proteins or polypeptides as desired.

**EXAMPLE 29** 

Assaying the Expressed Proteins or Polypeptides For Chemotactic/Chemokinetic Activity

The proteins or polypeptides of the present invention may also be evaluated for chemotactic/chemokinetic activity. For example, a protein or polypeptide of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for 35 example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins or polypeptides can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins or

polypeptides provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or polypeptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or polypeptide has the ability to directly stimulate directed movement of cells. Whether a particular protein or polypeptide has chemotactic activity for a population of cells can be readily determined by employing such protein or polypeptide in any known assay for cell chemotaxis.

The activity of a protein or polypeptide of the invention may, among other means, be measured by the following methods:

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Assays for chemotactic activity (which will identify proteins or polypeptides that induce or prevent chemotaxis) consist of assays that measure the ability of a protein or polypeptide to induce the migration of cells across a membrane as well as the ability of a protein or polypeptide to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience, Chapter 6.12: 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Mueller et al., Eur. J. Immunol. 25:1744-1748; Gruber et al. J. Immunol. 152:5860-5867, 1994; Johnston et al. J. Immunol., 153:1762-1768, 1994.

#### **EXAMPLE 30**

Assaying the Expressed Proteins or Polypeptides for Regulation of Blood Clotting

The proteins or polypeptides of the present invention may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Those proteins or polypeptides which are involved in the regulation of blood clotting may then

be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood

clotting is beneficial. For example, a protein or polypeptide of the invention may also exhibit hemostatic

or thrombolytic activity. As a result, such a protein or polypeptide is expected to be useful in treatment

of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance

coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other

causes. A protein or polypeptide of the invention may also be useful for dissolving or inhibiting

formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as

infarction of cardiac and central nervous system vessels (e.g., stroke)). Alternatively, as described in

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more detail below, nucleic acids encoding blood clotting activity proteins or polypeptides or nucleic acids regulating the expression of such proteins or polypeptides may be introduced into appropriate host cells to increase or decrease the expression of the proteins or polypeptides as desired.

**EXAMPLE 31** 

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# Assaying the Expressed Proteins or Polypeptides for Involvement in Receptor/Ligand Interactions

The proteins or polypeptides of the present invention may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those 10 skilled in the art, including the assays disclosed in the following references: Chapter 7, 7,28,1-7,28,22) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160, 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995; Gyuris et al., Cell 75:791-803, 1993.

For example, the proteins or polypeptides of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein or polypeptide of the present invention (including, without limitation, fragments of receptors and ligands) may be useful as inhibitors of receptor/ligand interactions. Alternatively, as described in more 25 detail below, nucleic acids encoding proteins or polypeptides involved in receptor/ligand interactions or nucleic acids regulating the expression of such proteins or polypeptides may be introduced into appropriate host cells to increase or decrease the expression of the proteins or polypeptides as desired.

#### **EXAMPLE 32**

Assaying the Proteins or Polypeptides for Anti-Inflammatory Activity

The proteins or polypeptides of the present invention may also be evaluated for antiinflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the 35 inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins or polypeptides exhibiting such activities can be used to treat inflammatory conditions

including chronic or acute conditions, including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome), ischemia-reperfusioninury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine- or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins or polypeptides of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material. Alternatively, as described in more detail below, nucleic acids encoding anti-inflammatory activity proteins or polypeptides or nucleic acids regulating the expression of such proteins or polypeptides may be introduced into appropriate host cells to increase or decrease the expression of the proteins or polypeptides as desired.

#### **EXAMPLE 33**

## Assaying the Expressed Proteins or Polypeptides for Tumor Inhibition Activity

The proteins or polypeptides of the present invention may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein or polypeptide of the invention may exhibit other anti-tumor activities. A protein or polypeptide may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein or polypeptide may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth. Alternatively, as described in more detail below, nucleic acids encoding proteins or polypeptides with tumor inhibition activity or nucleic acids regulating the expression of such proteins or polypeptides may be introduced into appropriate host cells to increase or decrease the expression of the proteins or polypeptides as desired.

A protein or polypeptide of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or climination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem

cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein. Alternatively, as described in more detail below, nucleic acids encoding proteins or polypeptides involved in any of the above mentioned activities or nucleic acids regulating the expression of such proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins or polypeptides as desired.

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#### **EXAMPLE 34**

# <u>Identification of Proteins or Polypeptides which Interact with</u> <u>Proteins or Polypeptides of the Present Invention</u>

Proteins or polypeptides which interact with the proteins or polypeptides of the present
invention, such as receptor proteins, may be identified using two hybrid systems such as the Matchmaker
Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the
kit, nucleic acids encoding the proteins or polypeptides of the present invention, are inserted into an
expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast
transcriptional activator GALA. cDNAs in a cDNA library which encode proteins or polypeptides which
might interact with the proteins or polypeptides of the present invention are inserted into a second
expression vector such that they are in frame with DNA encoding the activation domain of GALA. The
two expression plasmids are transformed into yeast and the yeast are plated on selection medium which
selects for expression of selectable markers on each of the expression vectors as well as GALA
dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine
are screened for GALA dependent lacZ expression. Those cells which are positive in both the histidine
selection and the lacZ assay contain plasmids encoding proteins or polypeptides which interact with the
proteins or polypeptides of the present invention.

Alternatively, the system described in Lustig et al., Methods in Enzymology 283: 83-99 (1997) may be used for identifying molecules which interact with the proteins or polypeptides of the present invention. In such systems, in vitro transcription reactions are performed on a pool of vectors containing nucleic acid inserts which encode the proteins or polypeptides of the present invention. The nucleic acid inserts are cloned downstream of a promoter which drives in vitro transcription. The resulting pools of mRNAs are introduced into Xenopus laevis oocytes. The oocytes are then assayed for a desired activity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for interaction with a known protein or polypeptide.

Proteins, polypeptides or other molecules interacting with proteins or polypeptides of the present invention can be found by a variety of additional techniques. In one method, affinity columns containing the protein or polypeptide of the present invention can be constructed. In some versions, of this method the affinity column contains chimeric proteins in which the protein or polypeptide of the present invention is fused to glutathione S-transferase. A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column. Molecules interacting with the protein or polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al. Electrophoresis, 18, 588-598 (1997). Alternatively, the molecules retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.

Molecules interacting with the proteins or polypeptides of the present invention can also be screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry, 246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein or polypeptide and other interacting molecules. Thus, it is possible to specifically select interacting molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethl dextran matrix) and a sample of test molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field (which extends a few hundred nanometers from the sensor surface). In these screening assays, the target molecule can be one of the proteins or polypeptides of the present invention and the test sample can be a collection of proteins, polypeptides or other molecules extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or chemical libraries, or phage displayed peptides. The tissues or cells from which the test molecules are extracted can originate from any species.

In other methods, a target protein or polypeptide is immobilized and the test population is a collection of unique proteins or polypeptides of the present invention.

To study the interaction of the proteins or polypeptides of the present invention with drugs, the microdialysis coupled to HPLC method described by Wang et al., Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch et al., J. Chromatogr. 777:311-328 (1997)can be used.

The system described in U.S. Patent No. 5,654,150 may also be used to identify molecules which interact with the proteins or polypeptides of the present invention. In this system, pools of nucleic acids encoding the proteins or polypeptides of the present invention are transcribed and translated in vitro and the reaction products are assayed for interaction with a known polypeptide or antibody.

It will be appreciated by those skilled in the art that the proteins or polypeptides of the present invention may be assayed for numerous activities in addition to those specifically enumerated above.

For example, the expressed proteins or polypeptides may be evaluated for applications involving control and regulation of inflammation, tumor proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins or polypeptides may be useful as nutritional agents or cosmetic agents.

The proteins or polypeptides of the present invention may be used to generate antibodies

5 capable of specifically binding to the proteins or polypeptides of the present invention. The
antibodies may be monoclonal antibodies or polyclonal antibodies. As used herein, "antibody" refers
to a polypeptide or group of polypeptides which are comprised of at least one binding domain, where
a binding domain is formed from the folding of variable domains of an antibody molecule to form
three-dimensional binding spaces with an internal surface shape and charge distribution

10 complementary to the features of an antigenic determinant of an antigen., which allows an
immunological reaction with the antigen. Antibodies include recombinant proteins comprising the
binding domains, as wells as fragments, including Fab, Fab', F(ab)2, and F(ab')2 fragments.

As used herein, an "antigenic determinant" is the portion of an antigen molecule, that determines the specificity of the antigen-antibody reaction. An "epitope" refers to an antigenic determinant of a polypeptide. An epitope can comprise as few as 3 amino acids in a spatial conformation which is unique to the epitope. Generally an epitope consists of at least 6 such amino acids, and more usually at least 8-10 such amino acids. Methods for determining the amino acids which make up an epitope include x-ray crystallography, 2-dimensional nuclear magnetic resonance, and epitope mapping e.g. the Pepscan method described by H. Mario Geysen et al. 1984. Proc. Natl. Acad. Sci. U.S.A. 81:3998-4002; PCT Publication No. WO 84/03564; and PCT Publication No. WO 84/03506.

In some embodiments, the antibodies may be capable of specifically binding to a protein or polypeptide encoded by EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids.

In some embodiments, the antibody may be capable of binding an antigenic determinant or an epitope in a protein or polypeptide encoded by EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids.

In other embodiments, the antibodies may be capable of specifically binding to an EST-related polypeptide, fragment of an EST-related polypeptide, positional segment of an EST-related polypeptide or fragment of a positional segment of an EST-related polypeptide. In some embodiments, the antibody may be capable of binding an antigenic determinant or an epitope in an EST-related polypeptide, fragment of an EST-related polypeptide, positional segment of an EST-related polypeptide or fragment of a positional segment of an EST-related polypeptide.

In the case of secreted proteins, the antibodies may be capable of binding a full-length protein encoded by a nucleic acid of the present invention, a mature protein (i.e. the protein generated by

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cleavage of the signal peptide) encoded by a nucleic acid of the present invention, or a signal peptide encoded by a nucleic acid of the present invention.

#### **EXAMPLE 35**

#### Production of an Antibody to a Human Polypeptide or Protein

The above described EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or nucleic acids encoding EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides or fragments of positional segments of 10 EST-related polypeptides are operably linked to promoters and introduced into cells as described above.

In the case of secreted proteins, nucleic acids encoding the full protein (i.e. the mature protein and the signal peptide), nucleic acids encoding the mature protein (i.e. the protein generated by cleavage of the signal peptide), or nucleic acids encoding the signal peptide are operably linked to promoters and introduced into cells as described above.

The encoded proteins or polypeptides are then substantially purified or isolated as described above. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few µg/ml. Monoclonal or polyclonal antibody to the protein or polypeptide can then be prepared as follows:

# 1. Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the proteins or polypeptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, and Milstein, Nature 256:495 (1975) or derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The 25 spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as 30 originally described by Engvall, Meth. Enzymol. 70:419 (1980). Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. in Basic Methods in Molecular Biology Elsevier, New York, Section 21-2.

# 2. Polyclonal Antibody Production by Immunization

Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein or 35 polypeptide can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom, which can be unmodified or modified to enhance immunogenicity. Effective

polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals response vary depending on site of inoculations and doses, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis. et al.J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against looknown concentrations of the antigen, begins to fall. See, for example, Ouchterlony, et al., Chap. 19 in: Handbook of Experimental Immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 μM). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either of the above protocols are useful in a variety of contexts. In particular, the antibodies may be used in immunoaffinity chromatography techniques such as those described below to facilitate large scale isolation, purification, or enrichment of the proteins or polypeptides encoded by EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or for the isolation, purification or enrichment of EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides or fragments of positional segments of EST-related polypeptides.

In the case of secreted proteins, the antibodies may be used for the isolation, purification, or
25 enrichment of the full protein (*i.e.* the mature protein and the signal peptide), the mature protein (*i.e.* the
protein generated by cleavage of the signal peptide), or the signal peptide are operably linked to
promoters and introduced into cells as described above.

Additionally, the antibodies may be used in immunoaffinity chromatography techniques such as those described below to isolate, purify, or enrich polypeptides which have been linked to the proteins or polypeptides encoded by EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or to isolate, purify, or enrich EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides or fragments of positional segments of EST-related polypeptides.

The antibodies may also be used to determine the cellular localization of polypeptides encoded by the proteins or polypeptides encoded by EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or the cellular

localization of EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides or fragments of positional segments of EST-related polypeptides.

In addition, the antibodies may also be used to determine the cellular localization of polypeptides which have been linked to the proteins or polypeptides encoded by EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or polypeptides which have been linked to EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides or fragments of positional segments of EST-related polypeptides.

The antibodies may also be used in quantitative immunoassays which determine concentrations
of antigen-bearing substances in biological samples; they may also used semi-quantitatively or
qualitatively to identify the presence of antigen in a biological sample or to identify the type of tissue
present in a biological sample. The antibodies may also be used in therapeutic compositions for killing
cells expressing the protein or reducing the levels of the protein in the body.

# 15 VI. Use of 5'ESTs or Consensus Contigated 5' ESTs or Sequences Obtainable Therefrom or Portions Thereof as Reagents

The EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids, may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

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1. Use of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids in isolation, diagnostic and forensic procedures

#### **EXAMPLE 36**

#### Preparation of PCR Primers and Amplification of DNA

The EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be used to prepare PCR primers for a variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. In some embodiments, the PCR primers at least 10, 15, 18, 20, 23, 25, 28, 30, 40, or 50 nucleotides in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to

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Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

10 EXAMPLE 37

Use of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids as probes

Probes derived from EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and may be made using techniques known in the art, including *in vitro* transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or *in vitro* transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or cDNA library which are capable of hybridizing to the detectable probe as described in Example 20 above.

PCR primers made as described in Example 36 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 38-42 below. Such analyses may utilize detectable probes or primers based on the sequences of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids.

In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids is then utilized in accordance with Example 36 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of 10 identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of 100 bases in length are used to prove identity between the suspect and the sample.

#### **EXAMPLE 39**

# Positive Identification by DNA Sequencing

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The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids. Preferably, 20 to 50 different primers are 20 used. These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with Example 34. Each of these DNA segments is sequenced, using the methods set forth in Example 36. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that 25 individual.

#### **EXAMPLE 40**

# Southern Blot Forensic Identification

The procedure of Example 38 is repeated to obtain a panel of at least 10 amplified sequences 30 from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple 35 duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with skill in the art. For a review of Southern blotting see Davis et al. (Basic Methods in Molecular Biology, 1986, Elsevier Press. pp 62-65).

A panel of probes based on the sequences of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis *et al.*, supra).

5 Preferably, the probe is at least 10, 12, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400 or 500 nucleotides in length. Preferably, the probes are at least 10, 12, 15, 18, 20, 25, 28, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400 or 500 nucleotides in length. In some embodiments, the probes are

Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

oligonucleotides which are 40 nucleotides in length or less.

# **EXAMPLE 41**

#### **Dot Blot Identification Procedure**

Another technique for identifying individuals using the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Probes are prepared that correspond to at least 10, preferably 50 sequences from the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids.

25 The probes are used to hybridize to the genomic DNA through conditions known to those in the art. The oligonucleotides are end labeled with P<sup>32</sup> using polynucleotide kinase (Pharmacia). Dot Blots are created by spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California). The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and hybridized with labeled probe using techniques known in the art (Davis et al., supra). The <sup>32</sup>P labeled DNA fragments are sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence and the DNA.

Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide mismatches (Wood et al., Proc. Natl. Acad. Sci. USA 82(6):1585-1588 (1985)). A unique pattern of dots distinguishes one individual from another individual.

35 EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids can be used as probes in the following alternative

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fingerprinting technique. In some embodiments, the probes are oligonucleotides which are 40 nucleotides in length or less.

Preferably, a plurality of probes having sequences from different EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids are used in the alternative fingerprinting technique. Example 42 below provides a representative alternative fingerprinting procedure in which the probes are derived from EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids.

10 EXAMPLE 42

# Alternative "Fingerprint" Identification Technique

Oligonucleotides are prepared from a large number, e.g. 50, 100, or 200, EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids using commercially available oligonucleotide services such as Genset, Paris,

15 France. Preferably, the oligonucleotides are at least 10, 15, 18, 20, 23, 25, 28, or 30 nucleotides in length. However, in some embodiments, the oligonucleotides may be more than 40, 50, 60 or 70 nucleotides in length.

Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and XbaI.

20 Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P<sup>32</sup>. The nitrocellulose is prehybridized with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

- In addition to their applications in forensics and identification, EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be mapped to their chromosomal locations. Example 41 below describes radiation hybrid (RH) mapping of human chromosomal regions using EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids.
- 35 Example 42 below describes a representative procedure for mapping EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids to their locations on human chromosomes. Example 43 below describes mapping of

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EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

5 2. Use of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids in Chromosome Mapping

#### **EXAMPLE 43**

Radiation hybrid mapping of EST-related nucleic acids, positional segments of

EST-related nucleic acids or fragments of positional segments of

10 EST-related nucleic acids to the human genome

Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different portions of the human genome. This technique is described by Benham et al. (Genomics 4:509-517, 1989) and Cox et al., (Science 250:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from a panel of 80-100 cell lines provides a mapping reagent for ordering EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids. In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler et al., Science 274:540-546, 1996).

RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thymidine kinase (TK) (Foster et al., Genomics 33:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr et al., Eur. J. Hum. Genet. 4:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers et al., Genomics 29:170-178, 1995), the region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer et al., Genomics 14:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington et al., Genomics 11:701-708, 1991).

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#### **EXAMPLE 44**

Mapping of EST-related nucleic acids, positional segments of

EST-related nucleic acids or fragments of positional segments of

EST-related nucleic acids to Human Chromosomes using PCR techniques

EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from EST-related

nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids to minimize the chance of amplifying through an intron. Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see Erlich. in PCR Technology; Principles and Applications for DNA Amplification. 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1 μCu of a 32P-labeled deoxycytidine triphosphate. The PCR is performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the 5'EST from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS PCRable DNA (BIOS Corporation) and NIGMS Human-Rodent Somatic Cell Hybrid Mapping Panel Number 1 (NIGMS, Camden, NJ).

PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given 5'EST. DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids. Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids will yield an amplified fragment. The 5'ESTs are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids. For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter et al., Genomics 6:475-481 (1990)).

Alternatively, the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be mapped to individual chromosomes using FISH as described in Example 45 below.

**EXAMPLE 45** 

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Mapping of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of

# EST-related nucleic acids to Chromosomes Using

#### Fluorescence In Situ Hybridization

Fluorescence in situ hybridization allows the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids 10 are obtained by FISH as described by Cherif et al. (Proc. Natl. Acad. Sci. U.S.A., 87:6639-6643, 1990). Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 µM) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BrdU, 0.1 mM) for 6 h. Colcemid (1 µg/ml) is added for the last 15 min before harvesting the cells. 15 Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCl (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research Laboratories, Bethesda, 20 MD), purified using a Sephadex G-50 column (Pharmacia, Upsala, Sweden) and precipitated. Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 X SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at -20°C are treated for 1 h at 37°C with RNase A (100 µg/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at 70°C, then dehydrated at 4°C. The slides are treated with proteinase K (10 µg/100 ml in 20 mM Tris-HCl, 2 mM CaCl<sub>2</sub>) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif et al., supra.). The slides are observed under a LEICA fluorescence microscope (DMRXA). Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be localized to a particular cytogenetic R-band on a given chromosome.

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Once the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids have been assigned to particular chromosomes using the techniques described in Examples 42-44 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

#### **EXAMPLE 46**

Use of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids to Construct or Expand Chromosome Maps

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the EST-related nucleic acids, positional 15 segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids are obtained. This approach is described in Ramajah Nagaraja et al., Genome Research 7:210-222, March 1997. Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the EST-related nucleic acids, positional segments of EST-related nucleic acids or 20 fragments of positional segments of EST-related nucleic acids whose position is to be determined. Once an insert has been found which includes the 5'EST, the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids was derived. This process can be 25 repeated for each insert in the YAC library to determine the location of each of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of ESTrelated nucleic acids relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms chromosomes may be obtained.

As described in Example 47 below EST-related nucleic acids, positional segments of ESTrelated nucleic acids or fragments of positional segments of EST-related nucleic acids may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

3. Use of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of 35 positional segments of EST-related nucleic acids Gene Identification

#### **EXAMPLE 47**

Identification of genes associated with hereditary diseases or drug response

This example illustrates an approach useful for the association of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids with particular phenotypic characteristics. In this example, a particular EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids is used as a test probe to associate that EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids with a particular phenotypic characteristic.

EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids are mapped to a particular location on a human chromosome using techniques such as those described in Examples 41 and 42 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids to be a very gene rich region containing several known genes and several diseases or phenotypes for which genes have not been identified. The gene corresponding to this EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids are used to screen genomic DNA, mRNA or cDNA obtained from the patients. EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids that are not amplified in the patients can be positively associated with a particular disease by further analysis. Alternatively, the .

25 PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating that the gene containing the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be responsible for the genetic disease.

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VII. Use of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids to Construct Vectors

The present EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes therein. Such secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by

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reducing the number of background proteins from which the desired protein must be purified or enriched. Exemplary secretion vectors are described in Example 48 below.

#### 1. Construction of secretion vectors

#### **EXAMPLE 48**

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# Construction of Secretion Vectors

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus promoter, the SV40 promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from one of the EST-related nucleic acids, positional segments of ESTrelated nucleic acids or fragments of positional segments of EST-related nucleic acids is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. Preferably, the signal sequence is from one of the nucleic acids of SEQ ID NOs.24-811. The host cell, tissue, or organism may be any cell, tissue, or organism which recognizes the signal 15 peptide encoded by the signal sequence in the EST-related nucleic acids, positional segments of ESTrelated nucleic acids or fragments of positional segments of EST-related nucleic acids. Suitable hosts include mammalian cells, tissues or organisms, avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins 20 which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal sequence such that a fusion protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, 25 be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Preferably, the secretion vector is maintained in multiple copies in each host cell. As used herein, multiple copies means at least 2, 5, 10, 20, 25, 50 or more than 50 copies per cell. In some embodiments, the multiple copies are maintained extrachromosomally. In other embodiments, the multiple copies result from amplification of a chromosomal sequence.

Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located 35 downstream of the gene inserted into the secretion vector.

After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant 5 using conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunoaffinitychromatography, size exclusion chromatography, ion exchange chromatography, and HPLC. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene encoding a protein whose secretion is desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein 15 expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

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#### **EXAMPLE 49**

#### **Fusion Vectors**

The EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of 20 positional segments of EST-related nucleic acids may be used to construct fusion vectors for the expression of chimeric polypeptides. The chimeric polypeptides comprise a first polypeptide portion and a second polypeptide portion. In the fusion vectors of the present invention, nucleic acids encoding the first polypeptide portion and the second polypeptide portion are joined in frame with one another so as to generate a nucleic acid encoding the chimeric polypeptide. The nucleic acid encoding the chimeric 25 polypeptide is operably linked to a promoter which directs the expression of an mRNA encoding the chimeric polypeptide. The promoter may be in any of the expression vectors described herein including those described in Examples 21 and 48.

Preferably, the fusion vector is maintained in multiple copies in each host cell. In some embodiments, the multiple copies are maintained extrachromosomally. In other embodiments, the 30 multiple copies result from amplification of a chromosomal sequence.

The first polypeptide portion may comprise any of the polypeptides encoded by the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids. In some embodiments, the first polypeptide portion may be one of the ESTrelated polypeptides, fragments of EST-related polypeptides, positional segments of EST-related 35 polypeptides, or fragments of positional segments of EST-related polypeptides.

The second polypeptide portion may comprise any polypeptide of interest. In some embodiments, the second polypeptide portion may comprise a polypeptide having a detectable

enzymatic activity such as green fluorescent protein or β galactosidase. Chimeric polypeptides in which the second polypeptide portion comprises a detectable polypeptide may be used to determine the intracellular localization of the first polypeptide portion. In such procedures, the fusion vector encoding the chimeric polypeptide is introduced into a host cell under conditions which facilitate the expression of 5 the chimeric polypeptide. Where appropriate, the cells are treated with a detection reagent which is visible under the microscope following a catalytic reaction with the detectable polypeptide and the cellular location of the detection reagent is determined. For example, if the polypeptide having a detectable enzymatic activity is β galactosidase, the cells may be treated with Xgal. Alternatively, where the detectable polypeptide is directly detectable without the addition of a detection reagent, the intracellular location of the chimeric polypeptide is determined by performing microscopy under conditions in which the dectable polypeptide is visible. For example, if the detectable polypeptide is green fluorescent protein or a modified version thereof, microscopy is performed by exposing the host cells to light having an appropriate wavelength to cause the green fluorescent protein or modified version thereof to fluoresce.

Alternatively, the second polypeptide portion may comprise a polypeptide whose isolation, purification, or enrichment is desired. In such embodiments, the isolation, purification, or enrichment of the second polypeptide portion may be achieved by performing the immunoaffinity chromatography procedures described below using an immunoaffinity column having an antibody directed against the first polypeptide portion coupled thereto.

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The proteins encoded by the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or the EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides, or fragments of positional segments of EST-related polypeptides may also be used to generate antibodies as explained herein in order to identify the tissue type or cell species from which a sample is derived as 25 described in Example 50.

#### **EXAMPLE 50**

# Identification of Tissue Types or Cell Species by Means of <u>Labeled Tissue Specific Antibodies</u>

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of antibody preparations as described herein which are conjugated, directly or indirectly to a detectable marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semi-qualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ion-exchange chromatography or by ammonium sulfate fractionation. Also, to provide

the most specific antisera, unwanted antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous antisera is suitable for either procedure.

# 5 1. Immunohistochemical Techniques

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Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in. Basic 503 Clinical Immunology, 3rd Ed. Lange, Los Altos, California (1980) or Rose, et al., Chap. 12 in: Methods in Immunodiagnosis, 2d Ed. John Wiley and Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below. Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen-antibody complexes achieved by means of an 15 electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example 125I, and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 µm, unfixed) of the unknown tissue and known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations 25 to provide a positive control, a negative control, for example, pre-immune sera, and a control for nonspecific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time 30 in a second antibody-antibody reaction, for example, by adding fluorescein- or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate 35 standards.

#### Identification of Tissue Specific Soluble Proteins 2.

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The visualization of tissue specific proteins and identification of unknown tissues from that procedure is carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction 10 concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. et al., Section 19-2 in: Basic Methods in Molecular Biology (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to 15 be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to 55 µl, and containing from about 1 to 100 µg protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. et al., 20 supra Section 19-3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or more specific antisera to tissue specific proteins prepared as described in Examples 20 and 33. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure described above a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-IgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin 30 conjugated marker. According to yet another strategy, enzyme labeled or radioactive protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

# **EXAMPLE 51**

# Immunohistochemical Localization of Polypeptides

The antibodies prepared as described herein above may be utilized to determine the cellular location of a polypeptide. The polypeptide may be any of the polypeptides encoded by EST-related

nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or the polypeptide may be one of the EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides, or fragments of positional segments of EST-related polypeptides. In some embodiments, the polypeptide may be a chimeric polypeptide such as those encoded by the fusion vectors of Example 49.

Cells expressing the polypeptide to be localized are applied to a microscope slide and fixed using any of the procedures typically employed in immunohistochemical localization techniques, including the methods described in *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. 1997. Following a washing step, the cells are contacted with the antibody. In some embodiments, the antibody is conjugated to a detectable marker as described above to facilitate detection. Alternatively, in some embodiments, after the cells have been contacted with an antibody to the polypeptide to be localized, a secondary antibody which has been conjugated to a detectable marker is placed in contact with the antibody against the polypeptide to be localized.

Thereafter, microscopy is performed under conditions suitable for visualizing the cellular location of the polypeptide.

The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, directed against the polypeptides encoded by EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or antibodies against the EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides, or fragments of positional segments of EST-related polypeptides, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign bodily sites.

The antibodies described herein may also be used in the immunoaffinity chromatography techniques described below to isolate, purify or enrich the polypeptides encoded by the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or to isolate, purify or enrich EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides, or fragments of positional segments of EST-related polypeptides. The immunoaffinity chromatography techniques described below may also be used to isolate, purify or enrich polypeptides which have been linked to the polypeptides encoded by the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or to isolate, purify or enrich polypeptides which have been linked to EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides, or fragments of positional segments of EST-related polypeptides, positional segments of EST-related polypeptides, or fragments of positional segments of EST-related polypeptides.

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# 127 EXAMPLE 52

# Immunoaffinity Chromatography

Antibodies prepared as described above are coupled to a support. Preferably, the antibodies are monoclonal antibodies, but polyclonal antibodies may also be used. The support may be any of those typically employed in immunoaffinity chromatography, including Sepharose CL-4B (Pharmacia, Piscataway, NJ), Sepharose CL-2B (Pharmacia, Piscataway, NJ), Affi-gel 10 (Biorad, Richmond, CA), or glass beads.

The antibodies may be coupled to the support using any of the coupling reagents typically used in immunoaffinity chromatography, including cyanogen bromide. After coupling the antibody to the support, the support is contacted with a sample which contains a target polypeptide whose isolation, purification or enrichment is desired. The target polypeptide may be a polypeptide encoded by the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related polypeptides, positional segments of EST-related polypeptides, fragments of EST-related polypeptides. The target polypeptides may also be polypeptides which have been linked to the polypeptides encoded by the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or the target polypeptides may be polypeptides which have been linked to EST-related nucleic acids or the target polypeptides may be polypeptides which have been linked to EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides, or fragments of positional segments of EST-related polypeptides using the fusion vectors described above.

Preferably, the sample is placed in contact with the support for a sufficient amount of time and under appropriate conditions to allow at least 50% of the target polypeptide to specifically bind to the antibody coupled to the support.

Thereafter, the support is washed with an appropriate wash solution to remove polypeptides which have non-specifically adhered to the support. The wash solution may be any of those typically employed in immunoaffinity chromatography, including PBS, Tris-lithium chloride buffer (0.1M lysine base and 0.5M lithium chloride, pH 8.0), Tris-hydrochloride buffer (0.05M Tris-hydrochloride, pH 8.0), or Tris/Triton/NaCl buffer (50mM Tris.cl, pH 8.0 or 9.0, 0.1% Triton X-100, and 0.5MNaCl).

After washing, the specifically bound target polypeptide is eluted from the support using the high pH or low pH elution solutions typically employed in immunoaffinity chromatography. In particular, the elution solutions may contain an eluant such as triethanolamine, diethylamine, calcium chloride, sodium thiocyanate, potasssium bromide, acetic acid, or glycine. In some embodiments, the elution solution may also contain a detergent such as Triton X-100 or octyl-\(\beta\)-D-glucoside.

The EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may also be used to clone sequences located upstream of the 5'ESTs which are capable of regulating gene expression, including promoter sequences, enhancer

sequences, and other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. Example 51 describes a method for cloning sequences upstream of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids.

# 2. Identification of upstream sequences with promoting or regulatory activities

# **EXAMPLE 53**

10 <u>Use of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids to Clone Upstream Sequences from Genomic DNA</u>

Sequences derived from EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which utilizes the GenomeWalker<sup>TM</sup> kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adapter primer provided in the kit and an outer gene specific primer. The gene specific primer should be selected to be specific for 5' EST of interest and should have a melting temperature, length, and location in the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5 μl of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2 μM each of outer adapter primer and outer gene specific primer, 1.1 mM of Mg(OAc)<sub>2</sub>, and 1 μl of the Tth polymerase 50X mix in a total volume of 50 μl. The reaction cycle for the first PCR reaction is as follows: 1 min at 94°C / 2 sec at 94°C, 3 min at 72°C (7 cycles) / 2 sec at 94°C, 3 min at 67°C (32 cycles) / 5 min at 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR

reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5 µl of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50 µl volume having a composition identical to that of the first PCR reaction except the nested primers are used. The first nested primer is specific for the adapter, and is provided with the GenomeWalker<sup>TM</sup>

kit. The second nested primer is specific for the particular EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids for which the promoter is to be cloned and should have a melting temperature, length, and location in

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the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids which is consistent with its use in PCR reactions.

The reaction parameters of the second PCR reaction are as follows: 1 min at 94°C / 2 sec at 94°C, 3 min at 72°C (6 cycles) / 2 sec at 94°C, 3 min at 67°C (25 cycles) / 5 min at 67°C. The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques.

Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic DNA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 10, 12, 15, 18, 20, 23, 25, 27, 30, 35, 40, or 50 nucleotides from the EST-related nucleic acids, positional 10 segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing the EST-related nucleic acids, positional segments of ESTrelated nucleic acids or fragments of positional segments of EST-related nucleic acids are isolated as described above. Thereafter, the single stranded DNA containing the EST-related nucleic acids, 15 positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids is released from the beads and converted into double stranded DNA using a primer specific for the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. cDNAs containing the 20 EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids are identified by colony PCR or colony hybridization.

Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as described in Example 54.

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#### **EXAMPLE 54**

# Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids are cloned into a suitable promoter reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, pβ-gal-Basic, pβ-gal35 Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase, β-galactosidase, or green fluorescent

protein. The sequences upstream of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the inserted upstream sequence.

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion.

The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

# **EXAMPLE 55**

# Cloning and Identification of Promoters

Using the method described in Example 54 above with 5' ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:15) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:16), the promoter having the internal designation P13H2 (SEQ ID NO:17) was obtained.

Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:18) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:19), the promoter having the internal designation P15B4 (SEQ ID NO:20) was obtained.

Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:21) and GAG ACC ACA CAG CTA GAC AA (SEQ ID NO:22), the promoter having the internal designation P29B6 (SEQ ID NO:23) was obtained.

Figure 4 provides a schematic description of the promoters isolated and the way they are

assembled with the corresponding 5' tags. The upstream sequences were screened for the presence of
motifs resembling transcription factor binding sites or known transcription start sites using the computer
program MatInspector release 2.0, August 1996.

Figure 5 describes the transcription factor binding sites present in each of these promoters. The columns labeled matrice provides the name of the MatInspector matrix used. The column labeled position provides the 5' position of the promoter site. Numeration of the sequence starts from the transcription site as determined by matching the genomic sequence with the 5' EST sequence. The column labeled "orientation" indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined by matching the genomic sequence with the sequence of the 5' EST. The column labeled "score" provides the MatInspector score found for this site. The column labeled "length" provides the length of the site in nucleotides. The column labeled "sequence" provides the sequence of the site found.

Bacterial clones containing plasmids containing the promoter sequences described above described above are presently stored in the inventor's laboratories under the internal identification numbers provided above. The inserts may be recovered from the deposited materials by growing an aliquot of the appropriate bacterial clone in the appropriate medium. The plasmid DNA can then be isolated using plasmid isolation procedures familiar to those skilled in the art such as alkaline lysis minipreps or large scale alkaline lysis plasmid isolation procedures. If desired the plasmid DNA may be further enriched by centrifugation on a cesium chloride gradient, size exclusion chromatography, or anion exchange chromatography. The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the inserted EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids. The PCR product which corresponds to the EST-related nucleic acids, positional segments of EST-related nucleic acids can then be manipulated using standard cloning techniques familiar to those skilled in the art.

The promoters and other regulatory sequences located upstream of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be used to design expression vectors capable of directing the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial, temporal, developmental, and quantitative patterns may be selected using the results of the expression analysis described above. For example, if a promoter which confers a high level of expression in muscle is desired, the promoter sequence upstream of EST-related nucleic acids,

positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids derived from an mRNA which are expressed at a high level in muscle, as determined by the methods above, may be used in the expression vector.

Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of the desired insert downstream of the promoter, such that the promoter is able to drive expression of the inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial 10 chromosomes.

Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression vector.

Following the identification of promoter sequences, proteins which interact with the promoter 15 may be identified as described in Example 56 below.

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#### **EXAMPLE 56**

# Identification of Proteins Which Interact with Promoter Sequences, Upstream Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are 25 transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art.

Nucleic acids encoding proteins which interact with sequences in the promoter may be identified 30 using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-Hybrid System kit available from Clontech (Catalog No. K1603-1). Briefly, the Matchmaker Onehybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem. A library 35 comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells

expressing the selectable marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or *in vitro* transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNAse protection analysis.

# VIII. Use of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids in Gene Therapy

The present invention also comprises the use of EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids in gene therapy strategies, including antisense and triple helix strategies as described in Examples 57 and 58 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

#### **EXAMPLE 57**

# Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids. The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex with sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., Ann. Rev. Biochem. 55:569-597 (1986) and Izant and Weintraub, Cell 36:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. The antisense molecules may be transcribed using *in vitro* transcription systems such as those which employ T7 or SP6 polymerase to

generate the transcript. Another approach involves transcription of the antisense nucleic acids *in vivo* by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be synthesized *in vitro*. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies are described by Rossi *et al.*, *Pharmacol. Ther.* **50(2)**:245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT WO94/23026 are used. In these molecules, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141 are used.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO 92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain "hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop" structures.

In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

Use of the closed antisense oligonucleotides disclosed in International Application No. WO
 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to

degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using *in vitro* expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between  $1 \times 10^{-10} M$  to  $1 \times 10^{-4} M$ . Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use *in vivo*. For example, an inhibiting concentration in culture of  $1 \times 10^{-7}$  translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi *et al.*, *supra*.

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In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

The EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it is associated with a particular gene. The EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids of the present invention or, more preferably, a portion of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies.

However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences from the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids are contemplated within the scope of this invention.

#### **EXAMPLE 58**

# Preparation and use of Triple Helix Probes

The sequences of the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris, France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran,

20 electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for altered cell function or reduced gene expression using techniques such as Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target gene in cells which have been treated with the oligonucleotide. The cell functions to be monitored are predicted based upon the homologies of the target genes corresponding to the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids from which the oligonucleotide were derived with known gene sequences that have been associated with a particular function. The cell functions can also be predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids are associated with the disease using techniques described herein.

The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced *in vivo* using the techniques described above and in Example 56 at a dosage calculated based on the *in vitro* results, as described in Example 57.

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In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to

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stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-971 (1989)).

#### **EXAMPLE 59**

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Use of EST-related nucleic acids, positional segments of

EST-related nucleic acids or fragments of positional segments of

EST-related nucleic acids to express an Encoded Protein in a Host Organism

The EST-related nucleic acids, positional segments of EST-related nucleic acids or fragments of positional segments of EST-related nucleic acids may also be used to express an encoded protein or polypeptide in a host organism to produce a beneficial effect. In addition, nucleic acids encoding the EST-related polypeptides, positional segments of EST-related polypeptides or fragments of positional segments of EST-related polypeptides may be used to express the encoded protein or polypeptide in a host organism to produce a beneficial effect.

In such procedures, the encoded protein or polypeptide may be transiently expressed in the host organism or stably expressed in the host organism. The encoded protein or polypeptide may have any of the activities described above. The encoded protein or polypeptide may be a protein or polypeptide which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

In some embodiments in which the protein or polypeptide is secreted, nucleic acids encoding the full length protein (i.e. the signal peptide and the mature protein), or nucleic acids encoding only the mature protein (i.e. the protein generated when the signal peptide is cleaved off) is introduced into the host organism.

The nucleic acids encoding the proteins or polypeptides may be introduced into the host organism using a variety of techniques known to those of skill in the art. For example, the extended 25 cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the nucleic acids encoding the protein or polypeptide may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene therapy, including viral or retroviral vectors. The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be introduced into cells *in vitro*. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein or polypeptide to produce a beneficial effect.

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#### **EXAMPLE 60**

The short core hydrophobic region (h) of signal peptides encoded by the sequences of SEQ ID NOs. 24-728 and 766-792 may also be used as a carrier to import a peptide or a protein of interest, so-called cargo, into tissue culture cells (Lin et al., J. Biol. Chem., 270: 14225-14258 (1995); Du et al., J. Peptide Res., 51: 235-243 (1998); Rojas et al., Nature Biotech., 16: 370-375 (1998)).

When cell permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the h region to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the extended cDNA sequence encoding the h region to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein-protein interactions involved in signal transduction pathways (Lin et al., supra; Lin et al., J. Biol. Chem., 271: 5305-5308 (1996); Rojas et al., J. Biol. Chem., 271: 27456-27461 (1996); Liu et al., Proc. Natl. Acad. Sci. USA, 93: 11819-11824 (1996); Rojas et al., Bioch. Biophys. Res. Commun., 234: 675-20680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense oligonucleotides or oligonucleotides designed to form triple helixes, as describedabove, in order to inhibit processing and maturation of a target cellular RNA.

#### **EXAMPLE 61**

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#### **Computer Embodiments**

As used herein the term "nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622" encompasses the nucleotide sequences of SEQ ID NOs. 24-811 and 1600-1622, fragments of SEQ ID NOs. 24-811 and 1600-1622, nucleotide sequences homologous to SEQ ID NOs. 24-811 and 1600-1622 or homologous to fragments of SEQ ID NOs. 24-811 and 1600-1622, and sequences

35 complementary to all of the preceding sequences. The fragments include portions of SEQ ID NOs. 24-811 and 1600-1622 comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of SEQ ID NOs. 24-811 and 1600-1622. Preferably, the fragments are novel

fragments. Preferably the fragments include polynucleotides described in Table II, polynucleotides described in Table III, polynucleotides described in Table IV or portions thereof comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive nucleotides of the polynucleotides described in Tables II, III, or IV. Homologous sequences and fragments of SEO ID 5 NOs. 24-811 and 1600-1622 refer to a sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, 80%, or 75% homology to these sequences. Homology may be determined using any of the computer programs and parameters described in Example 18, including BLAST2N with the default parameters or with any modified parameters. Homologous sequences also include RNA sequences in which unidines replace the thyrnines in the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622. The 10 homologous sequences may be obtained using any of the procedures described herein or may result from the correction of a sequencing error as described above. Preferably the homologous sequences and fragments of SEQ ID NOs. 24-811 and 1600-1622 include polynucleotides described in Table II. polynucleotides described in Table III, polynucleotides described in Table IV or portions thereof comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive 15 nucleotides of the polynucleotides described in Tables II, III, or IV. It will be appreciated that the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 can be represented in the traditional single character format (See the inside back cover of Styer, Lubert. Biochemistry, 3rd edition. W. H Freeman & Co., New York.) or in any other format which records the identity of the nucleotides in a sequence.

As used herein the term "polypeptide codes of SEQ ID NOS. 812-1599" encompasses the 20 polypeptide sequence of SEQ ID NOs. 812-1599 which are encoded by the 5' EST's of SEQ ID NOs. 24-811 and 1600-1622, polypeptide sequences homologous to the polypeptides of SEQ ID NOS. 812-1599, or fragments of any of the preceding sequences. Homologous polypeptide sequences refer to a polypeptide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, 80%, 75% homology to one of the polypeptide sequences of SEQ ID NOS. 812-1599. Homology may be determined using any 25 of the computer programs and parameters described herein, including FASTA with the default parameters or with any modified parameters. The homologous sequences may be obtained using any of the procedures described herein or may result from the correction of a sequencing error as described above. The polypeptide fragments comprise at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of the polypeptides of SEQ ID NOS. 812-1599. Preferably, the fragments are 30 novel fragments. Preferably, the fragments include polypeptides encoded by the polynucleotides described in Table II, or portions thereof comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids of the polypeptides encoded by the polynucleotides described in Table II. It will be appreciated that the polypeptide codes of the SEQ ID NOS. 812-1599 can be represented in the traditional single character format or three letter format (See the inside back cover of Starrier, Lubert. 35 Biochemistry, 3rd edition. W. H Freeman & Co., New York.) or in any other format which relates the identity of the polypeptides in a sequence.

It will be appreciated by those skilled in the art that the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 and polypeptide codes of SEQ ID NOS. 812-1599 can be stored, recorded, and manipulated on any medium which can be read and accessed by a computer. As used herein, the words "recorded" and "stored" refer to a process for storing information on a computer medium. A skilled artisan can readily adopt any of the presently known methods for recording information on a computer readable medium to generate manufactures comprising one or more of the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622, one or more of the polypeptide codes of SEQ ID NOS. 812-1599.

Another aspect of the present invention is a computer readable medium having recorded thereon at least 2, 5, 10, 15, 20, 25, 30, or 50 nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622. Another aspect of the present invention is a computer readable medium having recorded thereon at least 2, 5, 10, 15, 20, 25, 30, or 50 polypeptide codes of SEQ ID NOS. 812-1599.

Computer readable media include magnetically readable media, optically readable media, electronically readable media and magnetic/optical media. For example, the computer readable media may be a hard disk, a floppy disk, a magnetic tape, CD-ROM, Digital Versatile Disk (DVD), Random
15 Access Memory (RAM), or Read Only Memory (ROM) as well as other types of other media known to those skilled in the art.

Embodiments of the present invention include systems, particularly computer systems which store and manipulate the sequence information described herein. One example of a computer system 100 is illustrated in block diagram form in Figure 6. As used herein, "a computer system" refers to the hardware components, software components, and data storage components used to analyze the nucleotide sequences of the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622, or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 812-1599. In one embodiment, the computer system 100 is a Sun Enterprise 1000 server (Sun Microsystems, Palo Alto, CA). The computer system 100 preferably includes a processor for processing, accessing and manipulating the sequence data. The 25 processor 105 can be any well-known type of central processing unit, such as the Pentium III from Intel Corporation, or similar processor from Sun, Motorola, Compaq or International Business Machines.

Preferably, the computer system 100 is a general purpose system that comprises the processor 105 and one or more internal data storage components 110 for storing data, and one or more data retrieving devices for retrieving the data stored on the data storage components. A skilled artisan can readily appreciate that any one of the currently available computer systems are suitable.

In one particular embodiment, the computer system 100 includes a processor 105 connected to a bus which is connected to a main memory 115 (preferably implemented as RAM) and one or more internal data storage devices 110, such as a hard drive and/or other computer readable media having data recorded thereon. In some embodiments, the computer system 100 further includes one or more data retrieving device 118 for reading the data stored on the internal data storage devices 110.

The data retrieving device 118 may represent, for example, a floppy disk drive, a compact disk drive, a magnetic tape drive, etc. In some embodiments, the internal data storage device 110 is a

removable computer readable medium such as a floppy disk, a compact disk, a magnetic tape, etc. containing control logic and/or data recorded thereon. The computer system 100 may advantageously include or be programmed by appropriate software for reading the control logic and/or the data from the data storage component once inserted in the data retrieving device.

The computer system 100 includes a display 120 which is used to display output to a computer user. It should also be noted that the computer system 100 can be linked to other computer systems 125a-c in a network or wide area network to provide centralized access to the computer system 100.

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Software for accessing and processing the nucleotide sequences of the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622, or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 812-1599 (such as search tools, compare tools, and modeling tools etc.) may reside in main memory 115 during execution.

In some embodiments, the computer system 100 may further comprise a sequence comparer for comparing the above-described nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 or polypeptide codes of SEQ ID NOS. 812-1599 stored on a computer readable medium to reference nucleotide or polypeptide sequences stored on a computer readable medium. A "sequence comparer" refers to one or more programs which are implemented on the computer system 100 to compare a nucleotide or polypeptide sequence with other nucleotide or polypeptide sequences and/or compounds including but not limited to peptides, peptidomimetics, and chemicals stored within the data storage means. For example, the sequence comparer may compare the nucleotide sequences of the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622, or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 812-1599 stored on a computer readable medium to reference sequences stored on a computer readable medium to identify homologies, motifs implicated in biological function, or structural motifs. The various sequence comparer programs identified elsewhere in this patent specification are particularly contemplated for use in this aspect of the invention.

Figure 7 is a flow diagram illustrating one embodiment of a process 200 for comparing a new nucleotide or protein sequence with a database of sequences in order to determine the homology levels between the new sequence and the sequences in the database. The database of sequences can be a private database stored within the computer system 100, or a public database such as GENBANK, PIR OR SWISSPROT that is available through the Internet.

The process 200 begins at a start state 201 and then moves to a state 202 wherein the new sequence to be compared is stored to a memory in a computer system 100. As discussed above, the memory could be any type of memory, including RAM or an internal storage device.

The process 200 then moves to a state 204 wherein a database of sequences is opened for analysis and comparison. The process 200 then moves to a state 206 wherein the first sequence stored in the database is read into a memory on the computer. A comparison is then performed at a state 210 to determine if the first sequence is the same as the second sequence. It is important to note that this step is not limited to performing an exact comparison between the new sequence and the first sequence in the

database. Well-known methods are known to those of skill in the art for comparing two nucleotide or protein sequences, even if they are not identical. For example, gaps can be introduced into one sequence in order to raise the homology level between the two tested sequences. The parameters that control whether gaps or other features are introduced into a sequence during comparison are normally entered by 5 the user of the computer system.

Once a comparison of the two sequences has been performed at the state 210, a determination is made at a decision state 210 whether the two sequences are the same. Of course, the term "same" is not limited to sequences that are absolutely identical. Sequences that are within the homology parameters entered by the user will be marked as "same" in the process 200.

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If a determination is made that the two sequences are the same, the process 200 moves to a state 214 wherein the name of the sequence from the database is displayed to the user. This state notifies the user that the sequence with the displayed name fulfills the homology constraints that were entered. Once the name of the stored sequence is displayed to the user, the process 200 moves to a decision state 218 wherein a determination is made whether more sequences exist in the database. If no more sequences 15 exist in the database, then the process 200 terminates at an end state 220. However, if more sequences do exist in the database, then the process 200 moves to a state 224 wherein a pointer is moved to the next sequence in the database so that it can be compared to the new sequence. In this manner, the new sequence is aligned and compared with every sequence in the database.

It should be noted that if a determination had been made at the decision state 212 that the 20 sequences were not homologous, then the process 200 would move immediately to the decision state 218 in order to determine if any other sequences were available in the database for comparison.

Accordingly, one aspect of the present invention is a computer system comprising a processor, a data storage device having stored thereon a nucleic acid code of SEQ ID NOs. 24-811 and 1600-1622 or a polypeptide code of SEQ ID NOS, 812-1599, a data storage device having 25 retrievably stored thereon reference nucleotide sequences or polypeptide sequences to be compared to the nucleic acid code of SEQ ID NOs. 24-811 and 1600-1622 or polypeptide code of SEQ ID NOS. 812-1599 and a sequence comparer for conducting the comparison. The sequence comparer may indicate a homology level between the sequences compared or identify structural motifs in the above described nucleic acid code of SEQ ID NOs. 24-811 and 1600-1622 and polypeptide codes of 30 SEQ ID NOS. 812-1599 or it may identify structural motifs in sequences which are compared to these nucleic acid codes and polypeptide codes. In some embodiments, the data storage device may have stored thereon the sequences of at least 2, 5, 10, 15, 20, 25, 30, or 50 of the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 or polypeptide codes of SEQ ID NOS. 812-1599.

Another aspect of the present invention is a method for determining the level of homology 35 between a nucleic acid code of SEQ ID NOs. 24-811 and 1600-1622 and a reference nucleotide. sequence, comprising the steps of reading the nucleic acid code and the reference nucleotide sequence through the use of a computer program which determines homology levels and determining homology

between the nucleic acid code and the reference nucleotide sequence with the computer program. The computer program may be any of a number of computer programs for determining homology levels, including those specifically enumerated herein, including BLAST2N with the default parameters or with any modified parameters. The method may be implemented using the computer systems described 5 above. The method may also be performed by reading 2, 5, 10, 15, 20, 25, 30, or 50 of the above described nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 through use of the computer program and determining homology between the nucleic acid codes and reference nucleotide

sequences.

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Figure 8 is a flow diagram illustrating one embodiment of a process 250 in a computer for 10 determining whether two sequences are homologous. The process 250 begins at a start state 252 and then moves to a state 254 wherein a first sequence to be compared is stored to a memory. The second sequence to be compared is then stored to a memory at a state 256. The process 250 then moves to a state 260 wherein the first character in the first sequence is read and then to a state 262 wherein the first character of the second sequence is read. It should be understood that if the 15 sequence is a nucleotide sequence, then the character would normally be either A, T, C, G or U. If the sequence is a protein sequence, then it should be in the single letter amino acid code so that the first and sequence sequences can be easily compared.

A determination is then made at a decision state 264 whether the two characters are the same. If they are the same, then the process 250 moves to a state 268 wherein the next characters in the first 20 and second sequences are read. A determination is then made whether the next characters are the same. If they are, then the process 250 continues this loop until two characters are not the same. If a determination is made that the next two characters are not the same, the process 250 moves to a decision state 274 to determine whether there are any more characters either sequence to read.

If there aren't any more characters to read, then the process 250 moves to a state 276 wherein 25 the level of homology between the first and second sequences is displayed to the user. The level of homology is determined by calculating the proportion of characters between the sequences that were the same out of the total number of sequences in the first sequence. Thus, if every character in a first 100 nucleotide sequence aligned with a every character in a second sequence, the homology level would be 100%.

Alternatively, the computer program may be a computer program which compares the nucleotide sequences of the nucleic acid codes of the present invention, to reference nucleotide sequences in order to determine whether the nucleic acid code of SEQ ID NOs. 24-811 and 1600-1622 differs from a reference nucleic acid sequence at one or more positions. Optionally such a program records the length and identity of inserted, deleted or substituted nucleotides with respect to the sequence 35 of either the reference polynucleotide or the nucleic acid code of SEQ ID NOs. 24-811 and 1600-1622. In one embodiment, the computer program may be a program which determines whether the nucleotide sequences of the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 contain a biallelic marker

or single nucleotide polymorphism (SNP) with respect to a reference nucleotide sequence. This single nucleotide polymorphism may comprise a single base substitution, insertion, or deletion, while this biallelic marker may comprise abour one to ten consecutive bases substituted, inserted or deleted.

Another aspect of the present invention is a method for determining the level of homology between a polypeptide code of SEQ ID NOS. 812-1599 and a reference polypeptide sequence, comprising the steps of reading the polypeptide code of SEQ ID NOS. 812-1599 and the reference polypeptide sequence through use of a computer program which determines homology levels and determining homology between the polypeptide code and the reference polypeptide sequence using the computer program.

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Accordingly, another aspect of the present invention is a method for determining whether a nucleic acid code of SEQ ID NOs. 24-811 and 1600-1622 differs at one or more nucleotides from a reference nucleotide sequence comprising the steps of reading the nucleic acid code and the reference nucleotide sequence through use of a computer program which identifies differences between nucleic acid sequences and identifying differences between the nucleic acid code and the reference nucleotide 15 sequence with the computer program. In some embodiments, the computer program is a program which identifies single nucleotide polymorphisms. The method may be implemented by the computer systems described above and the method illustrated in Figure 8. The method may also be performed by reading at least 2, 5, 10, 15, 20, 25, 30, or 50 of the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 and the reference nucleotide sequences through the use of the computer program and identifying differences 20 between the nucleic acid codes and the reference nucleotide sequences with the computer program.

In other embodiments the computer based system may further comprise an identifier for identifying features within the nucleotide sequences of the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 812-1599.

An "identifier" refers to one or more programs which identifies certain features within the 25 above-described nucleotide sequences of the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 or the amino acid sequences of the polypeptide codes of SEQ ID NOS. 812-1599. In one embodiment, the identifier may comprise a program which identifies an open reading frame in the cDNAs codes of SEQ ID NOs. 24-811 and 1600-1622.

Figure 9 is a flow diagram illustrating one embodiment of an identifier process 300 for 30 detecting the presence of a feature in a sequence. The process 300 begins at a start state 302 and then moves to a state 304 wherein a first sequence that is to be checked for features is stored to a memory 115 in the computer system 100. The process 300 then moves to a state 306 wherein a database of sequence features is opened. Such a database would include a list of each feature's attributes along with the name of the feature. For example, a feature name could be "Initiation Codon" and the 35 attribute would be "ATG". Another example would be the feature name "TAATAA Box" and the feature attribute would be "TAATAA". An example of such a database is produced by the University of Wisconsin Genetics Computer Group (www.gcg.com).

Once the database of features is opened at the state 306, the process 300 moves to a state 308 wherein the first feature is read from the database. A comparison of the attribute of the first feature with the first sequence is then made at a state 310. A determination is then made at a decision state 316 whether the attribute of the feature was found in the first sequence. If the attribute was found, then the process 300 moves to a state 318 wherein the name of the found feature is displayed to the user.

The process 300 then moves to a decision state 320 wherein a determination is made whether move features exist in the database. If no more features do exist, then the process 300 terminates at an end state 324. However, if more features do exist in the database, then the process 300 reads the 10 next sequence feature at a state 326 and loops back to the state 310 wherein the attribute of the next feature is compared against the first sequence.

It should be noted, that if the feature attribute is not found in the first sequence at the decision state 316, the process 300 moves directly to the decision state 320 in order to determine if any more features exist in the database.

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In another embodiment, the identifier may comprise a molecular modeling program which determines the 3-dimensional structure of the polypeptides codes of SEQ ID NOS. 812-1599. In some embodiments, the molecular modeling program identifies target sequences that are most compatible with profiles representing the structural environments of the residues in known threedimensional protein structures. (See, e.g., Eisenberg et al., U.S. Patent No. 5,436,850 issued July 25, 20 1995). In another technique, the known three-dimensional structures of proteins in a given family are superimposed to define the structurally conserved regions in that family. This protein modeling technique also uses the known three-dimensional structure of a homologous protein to approximate the structure of the polypeptide codes of SEQ ID NOS. 812-1599. (See e.g., Srinivasan, et al., U.S. Patent No. 5,557,535 issued September 17, 1996). Conventional homology modeling techniques 25 have been used routinely to build models of proteases and antibodies. (Sowdhamini et al., Protein Engineering 10:207, 215 (1997)). Comparative approaches can also be used to develop threedimensional protein models when the protein of interest has poor sequence identity to template proteins. In some cases, proteins fold into similar three-dimensional structures despite having very weak sequence identities. For example, the three-dimensional structures of a number of helical 30 cytokines fold in similar three-dimensional topology in spite of weak sequence homology.

The recent development of threading methods now enables the identification of likely folding patterns in a number of situations where the structural relatedness between target and template(s) is not detectable at the sequence level. Hybrid methods, in which fold recognition is performed using Multiple Sequence Threading (MST), structural equivalencies are deduced from the threading output 35 using a distance geometry program DRAGON to construct a low resolution model, and a full-atom representation is constructed using a molecular modeling package such as QUANTA.

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According to this 3-step approach, candidate templates are first identified by using the novel fold recognition algorithm MST, which is capable of performing simultaneous threading of multiple aligned sequences onto one or more 3-D structures. In a second step, the structural equivalencies obtained from the MST output are converted into interresidue distance restraints and fed into the distance geometry program DRAGON, together with auxiliary information obtained from secondary structure predictions. The program combines the restraints in an unbiased manner and rapidly generates a large number of low resolution model confirmations. In a third step, these low resolution model confirmations are converted into full-atom models and subjected to energy minimization using the molecular modeling package QUANTA. (See e.g., Aszódi et al., Proteins: Structure, Function, and Genetics, Supplement 1:38-42 (1997)).

The results of the molecular modeling analysis may then be used in rational drug design techniques to identify agents which modulate the activity of the polypeptide codes of SEQ ID NOS. 812-1599.

Accordingly, another aspect of the present invention is a method of identifying a feature

within the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 or the polypeptide codes of

SEQ ID NOS. 812-1599 comprising reading the nucleic acid code(s) or the polypeptide code(s)

through the use of a computer program which identifies features therein and identifying features

within the nucleic acid code(s) or polypeptide code(s) with the computer program. In one

embodiment, computer program comprises a computer program which identifies open reading

frames. In a further embodiment, the computer program identifies structural motifs in a polypeptide

sequence. In another embodiment, the computer program comprises a molecular modeling program.

The method may be performed by reading a single sequence or at least 2, 5, 10, 15, 20, 25, 30, or 50 of
the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 or the polypeptide codes of SEQ ID

NOS. 812-1599 through the use of the computer program and identifying features within the nucleic

acid codes or polypeptide codes with the computer program.

The nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 or the polypeptide codes of SEQ ID NOS. 812-1599 may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 or the polypeptide codes of SEQ ID NOS. 812-1599 may be stored as text in a word processing file, such as MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or ORACLE. In addition, many computer programs and databases may be used as sequence comparers, identifiers, or sources of reference nucleotide or polypeptide sequences to be compared to the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 or the polypeptide codes of SEQ ID NOS. 812-1599. The following list is intended not to limit the invention but to provide guidance to programs and databases which are useful with the nucleic acid codes of SEQ ID NOs. 24-811 and 1600-1622 or the polypeptide codes of SEQ ID NOS. 812-1599. The programs and databases which may be used include, but are not limited to: MacPattern (EMBL).

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DiscoveryBase (Molecular Applications Group), GeneMine (Molecular Applications Group), Look (Molecular Applications Group), MacLook (Molecular Applications Group), BLAST and BLAST2 (NCBI), BLASTN and BLASTX (Altschul et al, J. Mol. Biol. 215: 403 (1990)), FASTA (Pearson and Lipman, Proc. Natl. Acad. Sci. USA, 85: 2444 (1988)), FASTDB (Brutlag et al. Comp. App. Biosci. 5 6:237-245, 1990), Catalyst (Molecular Simulations Inc.), Catalyst/SHAPE (Molecular Simulations Inc.), Cerius<sup>2</sup>.DBAccess (Molecular Simulations Inc.), HypoGen (Molecular Simulations Inc.), Insight II. (Molecular Simulations Inc.), Discover (Molecular Simulations Inc.), CHARMm (Molecular Simulations Inc.), Felix (Molecular Simulations Inc.), DelPhi, (Molecular Simulations Inc.), QuanteMM, (Molecular Simulations Inc.), Homology (Molecular Simulations Inc.), Modeler (Molecular Simulations 10 Inc.), ISIS (Molecular Simulations Inc.), Quanta/Protein Design (Molecular Simulations Inc.), WebLab (Molecular Simulations Inc.), WebLab Diversity Explorer (Molecular Simulations Inc.), Gene Explorer (Molecular Simulations Inc.), SeqFold (Molecular Simulations Inc.), the EMBL/Swissprotein database, the MDL Available Chemicals Directory database, the MDL Drug Data Report data base, the Comprehensive Medicinal Chemistry database, Derwents's World Drug Index database, the 15 BioByteMasterFile database, the Genbank database, and the Gensequ database. Many other programs and data bases would be apparent to one of skill in the art given the present disclosure.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turn-helix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, 20 sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.

### **EXAMPLE 62**

#### Methods of Making Nucleic Acids

25 The present invention also comprises methods of making the EST-related nucleic acids, fragments of EST-related nucleic acids, positional segments of the EST-related nucleic acids, or fragments of positional segments of the EST-related nucleic acids. The methods comprise sequentially linking together nucleotides to produce the nucleic acids having the preceding sequences. A variety of methods of synthesizing nucleic acids are known to those skilled in the art.

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In many of these methods, synthesis is conducted on a solid support. These included the 3' phosphoramidite methods in which the 3' terminal base of the desired oligonucleotide is immobilized on an insoluble carrier. The nucleotide base to be added is blocked at the 5' hydroxyl and activated at the 3' hydroxyl so as to cause coupling with the immobilized nucleotide base. Deblocking of the new immobilized nucleotide compound and repetition of the cycle will produce the desired 35 polynucleotide. Alternatively, polynucleotides may be prepared as described in U.S. Patent No. 5,049,656. In some embodiments, several polynucleotides prepared as described above are ligated together to generate longer polynucleotides having a desired sequence.

## **EXAMPLE 63**

## Methods of Making Polypeptides

The present invention also comprises methods of making the polynucleotides encoded by ESTrelated nucleic acids, fragments of EST-related nucleic acids, positional segments of the EST-related nucleic acids, or fragments of positional segments of the EST-related nucleic acids and methods of making the EST-related polypeptides, fragments of EST-related polypeptides, positional segments of EST-related polypeptides, or fragments of EST-related polypeptides. The methods comprise sequentially linking together amino acids to produce the nucleic polypeptides having the preceding sequences. In some embodiments, the polypeptides made by these methods are 150 amino acid or less in length. In other embodiments, the polypeptides made by these methods are 120 amino acids or less in length.

A variety of methods of making polypeptides are known to those skilled in the art, including methods in which the carboxyl terminal amino acid is bound to polyvinyl benzene or another suitable resin. The amino acid to be added possesses blocking groups on its amino moiety and any side chain reactive groups so that only its carboxyl moiety can react. The carboxyl group is activated with carbodiimide or another activating agent and allowed to couple to the immobilized amino acid. After removal of the blocking group, the cycle is repeated to generate a polypeptide having the desired sequence. Alternatively, the methods described in U.S. Patent No. 5,049,656 may be used.

As discussed above, the EST-related nucleic acids, fragments of the EST-related nucleic 20 acids, positional segments of the EST-related nucleic acids, or fragments of positional segments of the EST-related nucleic acids can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; production of secreted polypeptides or chimeric polypeptides, antibody production, as markers for tissues in which the 25 corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR 30 primers for genetic fingerprinting; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein or polypeptide which binds or potentially binds to another protein or polypeptide (such as, for example, in a receptor-ligand interaction), the polynucleotide 35 can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein or polypeptide with which binding occurs or to identify inhibitors of the binding interaction.

The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as 5 markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein or polypeptide binds or potentially binds to another protein or polypeptide (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins or polypeptides involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art.

References disclosing such methods include without limitation "Molecular Cloning; A Laboratory Manual," 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology; Guide to Molecular Cloning Techniques," Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins or polypeptides of the present invention can also be used as

nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid
supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In
such cases the protein or polynucleotide of the invention can be added to the feed of a particular
organism or can be administered as a separate solid or liquid preparation, such as in the form of powder,
pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of
the invention can be added to the medium in or on which the microorganism is cultured.

Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be limited only by reference to the appended claims.

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## Sequence Listing Free Text

The following free text appears in the accompanying Sequence Listing:

Von Heijne matrix

score

35 sequence

name

martinspector prediction

20

## 150 CLAIMS

- A purified nucleic acid comprising a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and sequences complementary to the sequences of SEO ID NOs. 24-811 and SEQ ID NOs. 1600-1622.
  - 2. A purified nucleic acid comprising at least 15 consecutive nucleotides of a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and sequences complementary to the sequences of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622.
- 3. A purified or isolated polypeptide comprising a sequence selected from the group consisting of the sequences of SEQ ID NOs. 812-1599.
  - 4. A method of making a cDNA comprising the steps of:
- a) contacting a collection of mRNA molecules from human cells with a primer comprising at least 15 consecutive nucleotides of a sequence selected from the group consisting of the sequences complementary to SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622;
  - b) hybridizing said primer to an mRNA in said collection that encodes said protein;
  - c) reverse transcribing said hybridized primer to make a first cDNA strand from said mRNA;
    - d) making a second cDNA strand complementary to said first cDNA strand; and
  - e) isolating the resulting cDNA comprising said first cDNA strand and said second cDNA strand.
- 5. A method of making a cDNA comprising the steps of:
  - a) obtaining a cDNA comprising a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622;
- b) contacting said cDNA with a detectable probe comprising at least 15 consecutive nucleotides of a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID
   NOs. 1600-1622 and the sequences complementary to SEQ ID NOs. 24-811 and SEQ ID NOs. 1600
  - c) identifying a cDNA which hybridizes to said detectable probe; and
  - d) isolating said cDNA which hybridizes to said probe.

1622 under conditions which permit said probe to hybridize to said cDNA;

- 35 6. A method of making a cDNA comprising the steps of:
  - a) contacting a collection of mRNA molecules from human cells with a first primer capable of hybridizing to the polyA tail of said mRNA;
    - b) hybridizing said first primer to said polyA tail;

- c) reverse transcribing said mRNA to make a first cDNA strand;
- d) making a second cDNA strand complementary to said first cDNA strand using at least one primer comprising at least 15 consecutive nucleotides of a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622; and
- e) isolating the resulting cDNA comprising said first cDNA strand and said second cDNA strand
  - 7. A method of making a polypeptide comprising the steps of:
- a) obtaining a cDNA which encodes a polypeptide encoded by a nucleic acid comprising
   10 a sequence selected from the group consisting of SEQ ID NOs. 24-811 or a cDNA which encodes a polypeptide comprising at least 10 consecutive amino acids of a polypeptide encoded by a sequence selected from the group consisting of SEQ ID NOs. 24-811;
  - b) inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter:
- 15 c) introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said cDNA; and
  - d) isolating said protein.
- 8. In an array of discrete ESTs or fragments thereof of at least 15 nucleotides in length, the improvement comprising inclusion in said array of at least one sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, the sequences complementary to the sequences of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and fragments comprising at least 15 consecutive nucleotides of said sequence.
- 9. The array of Claim 8 including therein at least five sequences selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, the sequences complementary to the sequences of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and fragments comprising at least 15 consecutive nucleotides of said sequences.
- 30 10. An enriched population of recombinant nucleic acids, said recombinant nucleic acids comprising an insert nucleic acid and a backbone nucleic acid, wherein at least 5% of said insert nucleic acids in said population comprise a sequence selected from the group consisting of SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622, the sequences complementary to SEQ ID NOs. 24-811 and SEQ ID NOs. 1600-1622 and fragments comprising at least 15 consecutive nucleotides of said sequences.
  - 11. An antibody composition capable of selectively binding to an epitope-containing fragment of a polypeptide comprising a contiguous span of at least 8 amino acids of any of SEQ ID NOs. 812-1599, wherein said antibody is polyclonal or monoclonal.

- 12. A computer readable medium having stored thereon a sequence selected from the group consisting of a nucleic acid code of SEQ ID NOs. 24-811 and 1600-1622 and a polypeptide code of SEO ID NOs. 812-1599.
- 13. A computer system comprising a processor and a data storage device wherein said data storage device has stored thereon a sequence selected from the group consisting of a nucleic acid code of SEQID NOs. 24-811 and 1600-1622 and a polypeptide code of SEQ ID NOs. 812-1599.
- 10 14. The computer system of Claim 13 further comprising a sequence comparer and a data storage device having reference sequences stored thereon.
  - 15. The computer system of Claim 14 wherein said sequence comparer comprises a computer program which indicates polymorphisms.
  - 16. The computer system of Claim 13 further comprising an identifier which identifies features in said sequence.
- 17. A method for comparing a first sequence to a reference sequence wherein said first sequence is selected from the group consisting of a nucleic acid code of SEQID NOs. 24-811 and 1600-1622 and a polypeptide code of SEQ ID NOs. 812-1599 comprising the steps of:
  - a) reading said first sequence and said reference sequence through use of a computer program which compares sequences; and
- b) determining differences between said first sequence and said reference sequence with
   25 said computer program.
  - 18. The method of Claim 17, wherein said step of determining differences between the first sequence and the reference sequence comprises identifying polymorphisms.
- 19. A method for identifying a feature in a sequence selected from the group consisting of a nucleic acid code of SEQID NOs. 24-811 and 1600-1622 and a polypeptide code of SEQ ID NOs. 812-1599 comprising the steps of:
  - a) reading said sequence through the use of a computer program which identifies features in sequences; and
- b) identifying features in said sequence with said computer program.
  - 20. A vector comprising a nucleic acid according to either Claims 1 or 2.
  - 21. A host cell containing a nucleic acid of Claim 20.

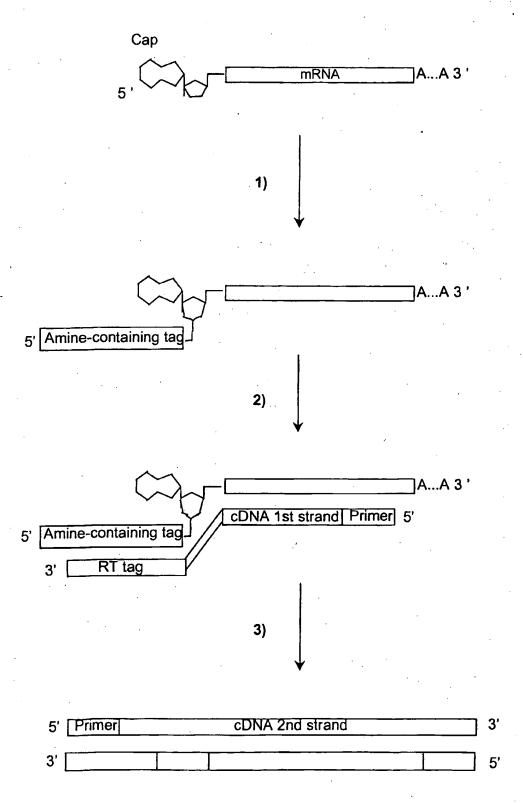


Figure 1

Minimum signal peptide score	false positive rate	false negative rate	proba(0.1)	proba(0.2)
3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0.93
9,5	0,007	0,581	0,863	0,934
10	0,006	0,679	0,835	0,919

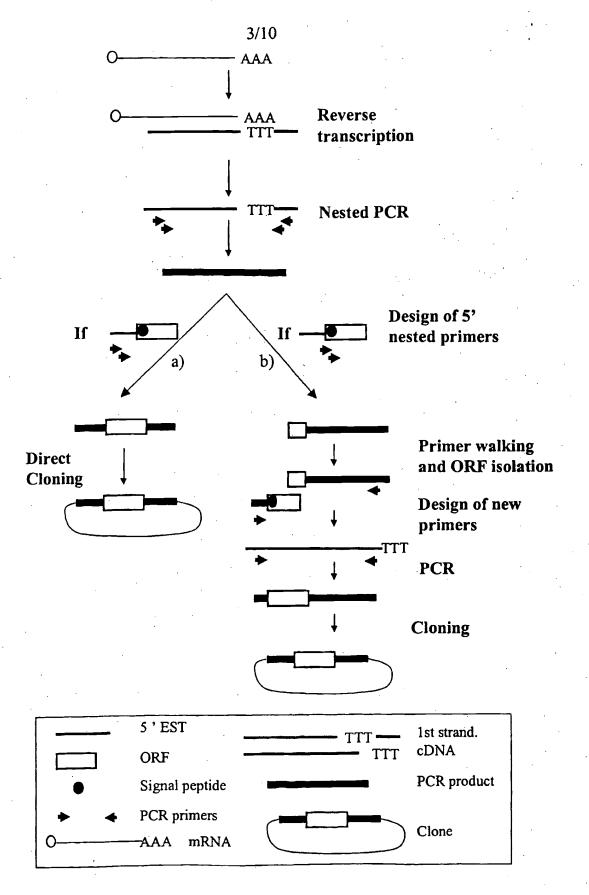


Figure 3

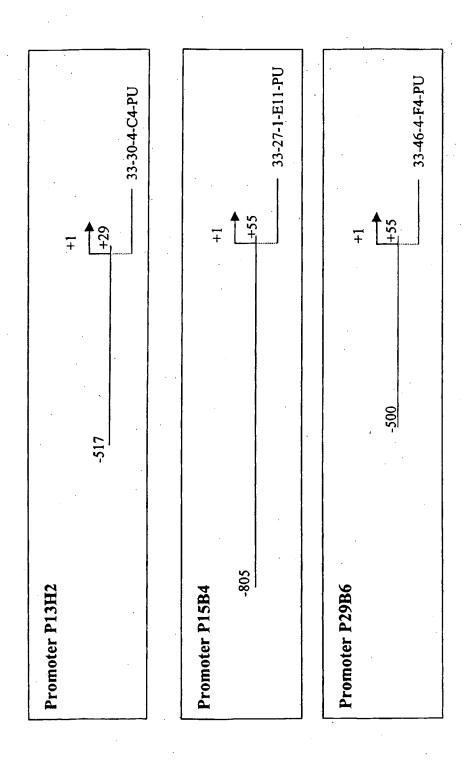


Figure 4

5/10

# Promoter sequence P13H2 (546 bp):

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MYOD_Q6	-501	-	0.961	10	CCCAACTGAC
S8_01	-444	-	0.960	· 11 1	AATAGAATTAG
S8_01	-425	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390		0.960	11	GCACACCTCAG
GATA_C	-364	-	0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHAE47_01	-235		0.973	16	CATAACAGATGGTAAG
TAL1BETAE47_01	-235		0.983	16	CATAACAGATGGTAAG
TAL1BETAITF2_01	-235		0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	•	0.954	10	ACCATCTGTT
GATA1_04	-217	-	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123		0.962	10	TGGGAATTCC
GATA1_02	-96		0.950	14	TCAGTGATATGGCA
SRY_02	-41	-	0.951	12	TAAAACAAAACA
E2F_02	-33	+	0.957	8	TTTAGCGC
MZF1_01	-5	•	0.975	8	TGAGGGGA

## Promoter sequence P15B4 (861bp):

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CMYB_01	-684	+	0.994	9	TGACCGTTG
VMYB_02	-682	-	0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCCTGGAA
STAT_01	-673	-	0.951	9	TTCCAGGAA
MZF1_01	-556	•	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTC
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	-	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190		0.981	10	AGCATCTGCC
DELTAEF1_01	-176		0.958	11	TCCCACCTTCC
S8_01	5		0.992	11	GAGGCAATTAT
M7F1 01	16		0.986	. 8	AGAGGGGA

## Promoter sequence P29B6 (555 bp):

		_			
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NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	-	0.985	12	CAGCACGTGAGT
NMYC_01	-309		0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	-	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	. 8	TCACGTGC
USF_C	-307	~	0.991	8	GCACGTGA
MZF1_01	-292	-	0.968	8	CATGGGGA
ELK1_02	-105		0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102		Ó.974	10	TCCGGAAGCC
AP1_Q4	-42		0.963	11	AGTGACTGAAC
AP1FJ_Q2	-42		0.961	11	AGTGACTGAAC
PADS_C	45		1.000	9	TGTGGTCTC

Figure 5

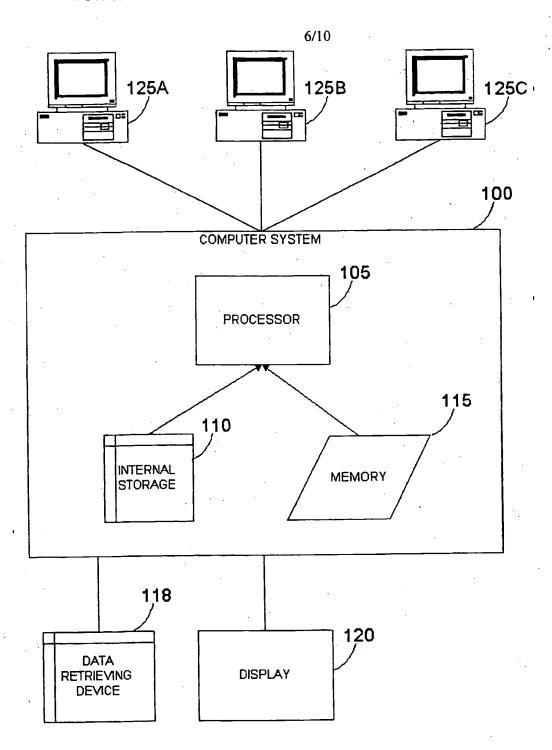


FIGURE 6

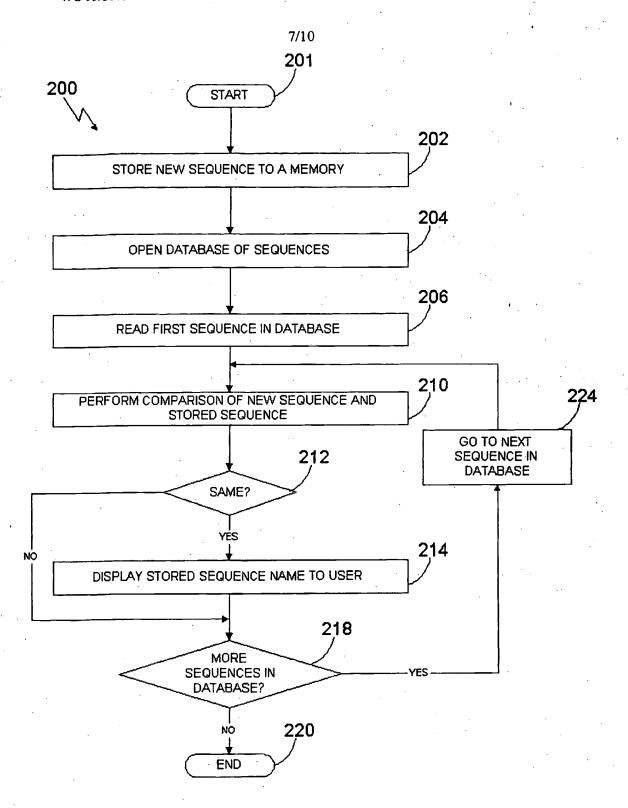
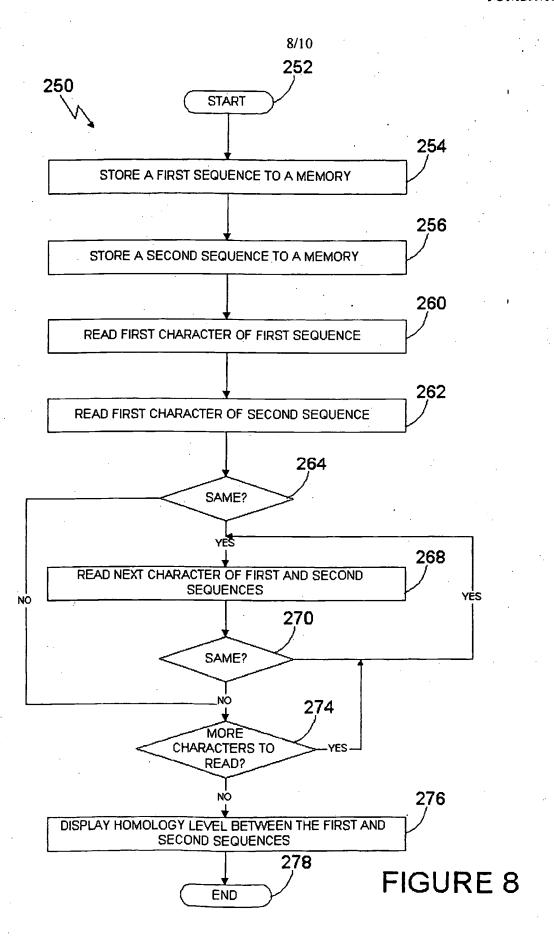
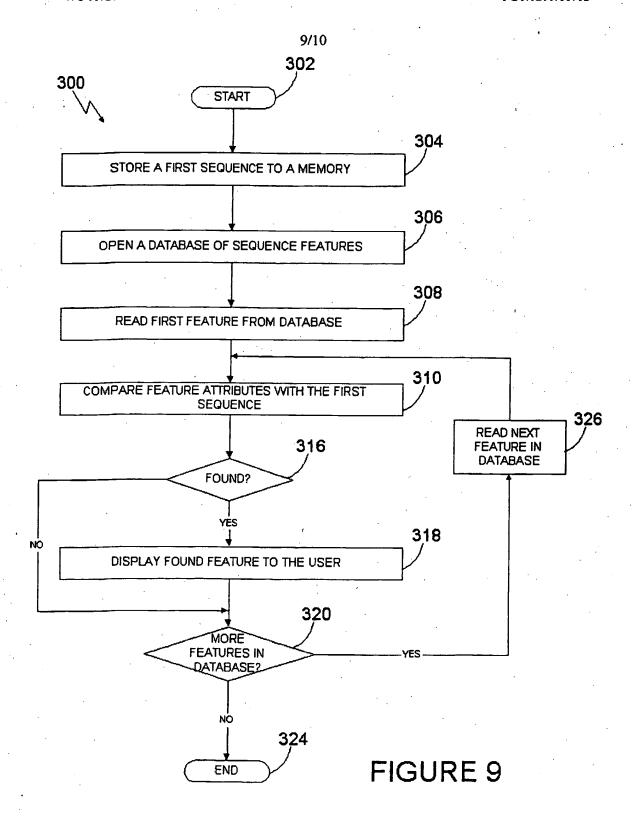


FIGURE 7





	Search characteristic	istic			Colontina	
Step	Program	Strand	Parameters	Identity (%) I anoth (ha)	I anoth (ha)	oriention Characteristics
miscellanaeous	FASTA	both		06	15	Comments
tRNA	FASTA	Но		Co		
		3		00	90	
rKNA	BLASTN	both	S=108	80	40	
mtRNA	BLASTN	both	S=108	80	40	
Procaryotic	BLASTN	both	S=144	06	40	
Fungal	BLASTN	both	S=144	06	40	
Alu	BLASTN	both	S=72, B=5	70	40	max 5 matches masking
L1	BLASTN	both	S=72, B=5	20	40	max 5 matches, masking
Repeats	BLASTN	both	S=72	70	40	masking
•			W=6, S=10, E=1000,			D
PolyA	BLAST2N	top	N=12	06	01	in the last 100 nucleotides
Polyadenylation signal	•	top	AATAAA allowing 1 mismatch	owing 1 mism	latch	in the 50 nucleotides before the 5' end of the polA
Vertebrate	<b>BLASTN</b> then FASTA	both	•	90 then 70	30	first BLASTN, then FASTA on maching sequences
ESTs	BLAST2N	both	•	.06	30	
Genesed	BLASTN	both	W=8, B=10	8	30	
ORF	BLASTP	top	W=8, B=10			on ORF proteins, max 10 matches
Proteins	BLASTX	top	E = 0.001	70	30	

Figure 10

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                            -10
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                   -80
                                         -75
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ctt cct gaa tta ttt cag tgt cat ggt act gca gat gag tta gtt ctt
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Leu Pro Glu Leu Phe Gln Cys His Gly Thr Ala Asp Glu Leu Val Leu
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cat tot tgg gca gaa gag aca aac tca atg tta aaa tot cta gga gtg
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His Ser Trp Ala Glu Glu Thr Asn Ser Met Leu Lys Ser Leu Gly Val
                            35
acc acg aag ttt cat agt ttt cca aat gtt tac cat gag cta agc aaa
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Thr Thr Lys Phe His Ser Phe Pro Asn Val Tyr His Glu Leu Ser Lys
                        50
act gag tta gac ata ttg aag tta tgg att ctt aca aag ctg cca gga
                                                                      717
Thr Glu Leu Asp Ile Leu Lys Leu Trp Ile Leu Thr Lys Leu Pro Gly
                    65 ·
                                        70
gaa atg gaa aaa caa aaa tgaatgaatc aagagtgatt tgttaatgta
                                                                      765
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Glu Met Glu Lys Gln Lys
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 taagaaatag caaaaaaaa aaaaaaa
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                                  -80
                                                      -75
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                                                  -60
 Leu Thr Asp Leu Ile Asp Glu Glu Val Lys Ser Gly Ile Lys Lys Asn
                          -50
 Arg Ile Leu Ile Gly Gly Phe Ser Met Gly Gly Cys Met Ala Met His
 -40
                      -35
                                          -30
 Leu Ala Tyr Arg Asn His Gln Asp Val Ala Gly Val Phe Ala Leu Ser
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                                      -15
 Ser Phe Leu Asn Lys Ala Ser Ala Val Tyr Gln Ala Leu Gln Lys Ser
 Asn Gly Val Leu Pro Glu Leu Phe Gln Cys His Gly Thr Ala Asp Glu
     10
 Leu Val Leu His Ser Trp Ala Glu Glu Thr Asn Ser Met Leu Lys Ser
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 Leu Gly Val Thr Thr Lys Phe His Ser Phe Pro Asn Val Tyr His Glu
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 ctg ccc tgg gag gac ggc agg tcc ggg ttg ctc tcc ggc ggc ctc cct
                                                                       101
 Leu Pro Trp Glu Asp Gly Arg Ser Gly Leu Leu Ser Gly Gly Leu Pro
                 -35
                                     -30
 egg aag tgt tee gte tte cae etg tte gtg gee tge ete teg etg gge
                                                                       149
 Arg Lys Cys Ser Val Phe His Leu Phe Val Ala Cys Leu Ser Leu Gly
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									٥	'							
			-20					-15					-10				
ttc	ttc	tcc	cta	ctc	tgg	ctg	cag	ctc	agc	tgc	tct	ggg	gac	gtg	gcc		197
Phe	Phe	Ser	Leu	Leu	Trp	Leu	Gln	Leu	Ser	Cys	Ser	Gly	Asp	Val	Ala		•
		-5					1			•	5		•				
Caa	aca	atc	agg	qqa	caa	aaa	caq	gag	acc	tca	aac	cct	CCC	cgt	acc	1	245
Ara	Δla	Val	Ara	Glv	Gln	Glv	Gln	Glu	Thr	Ser	G) A	Pro	Dro	Arg	פומ	•	2.13
10	AIG	• • • •	••••	,	15	01,	01	O14	1	20	GIY	110	FIO	ALG	2.5		•
			~~~			aa+	~~~					_:_					
tgc	CCC	cca	gag	ccg	- 666	CCT	gag	cac	Egg	gaa	gaa	gac	gca	tcc	Egg		293
Cys	Pro	Pro	GIU		Pro	Pro	Glu	Hıs	Trp	Glu	Glu	Asp	Ala	Ser	Trp		
•				30					35					40			
ggc	CCC	cac	cgc	ctg	gca	gtg	ctg	gtg	CCC	ttc	cgc	gaa	cgc	ttc	gag		341
Gly	Pro	His	Arg	Leu	Ala	Val	Leu	Val	Pro	Phe	Ara	Glu	Arg	Phe	Glu		
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																	303
GIU	ren		Val	Pile	vaı	PIO		met	Arg	Arg	Pne		ser	Arg	гÀг		
		60		•			65					70					
														ttc			437
Lys	Ile	Arg	His	His	Ile	Tyr	Val	Leu	Asn	Gln	Val	Asp	His	Phe	Arg		
	75			•		80					85						
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														Ser			
90					95				01,	100	200	014	001	001	105		
		~~~	+=0	2++		2+~			~								<b>-</b>
agc	acg	gac	Tac.	41L	900	aig	cac	gac	gtt	gac	ctg	CEC	CCE	ctc	aac		533
Ser	Inr	Asp	ıyr		Ala	met	Hls	Asp		Asp	Leu	Leu	Pro	Leu	Asn		
				110					115					120			
gag	gag	ctg	gac	tat	ggc	ttt	cct	gag	gct	999	CCC	ttc	cac	gtg	gcc		581
Glu	Glu	Leu	Asp	Tyr	Gly	Phe	Pro	Glu	Ala	Gly	Pro	Phe	His	Val	Ala		
			125					130		_			135				
tcc	ccq	qaq	ctc	cac	cct	ctc	tac	cac	tac	aaq	acc.	tat	atc	ggc	aac		629
														Gly			
001	110	140					145		- , -	цуз	****	150	•	O1 y	Cly		
			at a		222												
															tcc		677
116		Leu	Leu	ser	гÀè		HIS	Tyr	Arg.	Leu		Asn	GIY	Met	ser		
	155					160					165						
aac	cgc	ttc	tgg	ggc.	tgg	ggc	cgc	gag	gac	gac	gag	ttc	tac	cgg	cgc		725
Asn	Arg	Phe	Trp	Gly	Trp	Gly	Arg	Glu	Asp	Asp	Glu	Phe	Tyr	Arg	Arg		
170					175				-	180			_	_	185		
att	aaq	gga	act	qqq	ctc	caq	ctt	ttc	cac	CCC	tca	aaa	atc	aca	act		773
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Gly	Tyr	Lys		Pne	Arg	His	Leu	His	Asp	Pro	Ala	Trp	Arg	Lys	Arg		
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gac	cag	aag	cgc	atc	gca	gct	caa	aaa	cag	gag	cag	ttc	aag	gtg	gac		869
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•		220	_				225	-				230	-		•		
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Arg		GIY	Gry	Leu	ASII		Val	гÀР	ıyı	nis		MIG	Ser	Arg	1111		
	235					240					245						
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Leu Gln Leu Ser Cys Ser Gly Asp Val Ala Arg Ala Val Arg Gly Gln
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Gly Gln Glu Thr Ser Gly Pro Pro Arg Ala Cys Pro Pro Glu Pro Pro
Pro Glu His Trp Glu Glu Asp Ala Ser Trp Gly Pro His Arg Leu Ala
Val Leu Val Pro Phe Arg Glu Arg Phe Glu Glu Leu Leu Val Phe Val
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Pro His Met Arg Arg Phe Leu Ser Arg Lys Lys Ile Arg His His Ile
Tyr Val Leu Asn Gln Val Asp His Phe Arg Phe Asn Arg Ala Ala Leu
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Ile Asn Val Gly Phe Leu Glu Ser Ser Asn Ser Thr Asp Tyr Ile Ala
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                                    105
Met His Asp Val Asp Leu Leu Pro Leu Asn Glu Glu Leu Asp Tyr Gly
                                120.
Phe Pro Glu Ala Gly Pro Phe His Val Ala Ser Pro Glu Leu His Pro
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Leu Tyr His Tyr Lys Thr Tyr Val Gly Gly Ile Leu Leu Leu Ser Lys
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Gln His Tyr Arg Leu Cys Asn Gly Met Ser Asn Arg Phe Trp Gly Trp
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Gly Arg Glu Asp Asp Glu Phe Tyr Arg Arg Ile Lys Gly Ala Gly Leu
Gln Leu Phe Arg Pro Ser Gly Ile Thr Thr Gly Tyr Lys Thr Phe Arg
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His Leu His Asp Pro Ala Trp Arg Lys Arg Asp Gln Lys Arg Ile Ala
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Thr Val Lys Tyr His Val Ala Ser Arg Thr Ala Leu Ser Val Gly Gly
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cag gga ctg caa ggc tgg aag tcc ggt ggg gac cgt ggc tgt ggc ctt 254 Gln Gly Leu Gln Gly Trp Lys Ser Gly Gly Asp Arg Gly Cys Gly Leu -260 -255 caa gag agt gag cct gaa gat ttc ttg aag ctt ttc att gat ccc aat 302 Gln Glu Ser Glu Pro Glu Asp Phe Leu Lys Leu Phe Ile Asp Pro Asn

-245 -240 gag gtg tac tgc tca gaa gca tct cct ggc agt gac agt ggc atc tct 350 Glu Val Tyr Cys Ser Glu Ala Ser Pro Gly Ser Asp Ser Gly Ile Ser -230 -225

gag gac ted tgc cat cca gac agt ecc cet gee ecc agg gea acc agt 398 Glu Asp Ser Cys His Pro Asp Ser Pro Pro Ala Pro Arg Ala Thr Ser ~215 -210

tct cct atg ctc tat gag gtt gtc tat gag gca ggg gcc ctg gag agg 446 Ser Pro Met Leu Tyr Glu Val Tyr Glu Ala Gly Ala Leu Glu Arg -200 -195

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gat cag tgg agc cca gca ttt atg gtg cct gat tcc tgc atg gtc agt 542 Asp Gln Trp Ser Pro Ala Phe Met Val Pro Asp Ser Cys Met Val Ser -170 -165 -160

gag ctg ccc ttt gat gct cat gcc cac atc ctg ccc aga gca ggc acc 590 Glu Leu Pro Phe Asp Ala His Ala His Ile Leu Pro Arg Ala Gly Thr -150 -145

gta gcc cca gtg ccc tgt aca acc ctg ctg ccc tgt caa acc ctg ttc 638 Val Ala Pro Val Pro Cys Thr Thr Leu Leu Pro Cys Gln Thr Leu Phe

-135 -130 ctg acc gat gag gag aag cgt ctg ctg ggg cag gaa ggg gtt tcc ctg 686 Leu Thr Asp Glu Glu Lys Arg Leu Leu Gly Gln Glu Gly Val Ser Leu

-115 -110 cee tet cae etg eec etc ace aag gea gag gag agg gte etc aag aag 734

Pro Ser His Leu Pro Leu Thr Lys Ala Glu Glu Arg Val Leu Lys Lys -105 -100 -95

gtc agg agg aaa atc cgt aac aag cag tca gct cag gac agt cgg cgg 782 Val Arg Arg Lys Ile Arg Asn Lys Gln Ser Ala Gln Asp Ser Arg Arg -85 -80

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cac aac atc tcc ttg gta gct cag ctc cgc cag ctg cag acg cta att 926

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gct caa act too aac aaa gct gcc cag acc agc act tgt gtt ttg a	tt 974
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Leu Leu Phe Ser Leu Ala Leu Ile Ile Leu Pro Ser Phe Ser Pro P	·
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Gln Ser Arg Pro Glu Ala Gly Ser Glu Asp Tyr Gln Pro His Gly V 10 15 20	al
10 15 20 act tcc aga aat atc ctg acc cac aag gac gta aca gaa aat ctg g	ag 1118
Thr Ser Arg Asn Ile Leu Thr His Lys Asp Val Thr Glu Asn Leu G	
25 30 35	
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Ala Asn Gly Ser Thr Arg Thr Leu Leu Glu Lys Met Gly Gly Lys P	
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Arg Pro Ser Gly Arg Ile Arg Ser Val Leu His Ala Asp Glu Met	1237
75 80 85	
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Tyr Ile Asp Gly Leu Glu Ser Arg Val Ala Ala Cys Ser Ala Gln Asn
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Gln Glu Leu Gln Lys Lys Val Gln Glu Leu Glu Arg His Asn Ile Ser
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gataggacat tgatagatac ataagtacca ggacaaaagc agggagatct tttttccaaa
                                                                       240
atcaggagaa aaaaatgaca tctggaaaac ctatagggaa aggcataaca gatggtaagg
                                                                       300
atactttatc ttgagtagga gagccttcct gtggcaacgt ggagaaggga agaggtcgta
                                                                       360
gaattgagga gtcagctcag ttagaagcag ggagttggga attccgttca tgtgatttag
                                                                       420
catcagtgat atggcaaatg tgggactaag ggtagtgatc agagggttaa aattgtqtgt
                                                                       480
tttgttttag cgctgctggg gcatcgcctt gggtcccctc aaacagattc ccatgaatct
                                                                       540
cttcat
                                                                       546 .
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     score 0.956
     sequence ggaccaatcat
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score 0.962 sequence cctgggga

- <221> protein\_bind
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   score 0.994
   sequence tgaccgttg
- <221> protein\_bind
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- <223> matinspector prediction
   name VMYB\_02
   score 0.985
   sequence tccaacggt
- <221> protein bind
- <222> 135..143
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   score 0.968
   sequence ttcctggaa
- <221> protein\_bind
- <222> complement(135..143)
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- <223> matinspector prediction name MZF1\_01 score 0.956 sequence ttggggga
- <221> protein\_bind
- <222> 357..368
- <223> matinspector prediction name IK2\_01 score 0.965 sequence gaatgggatttc
- <221> protein\_bind
- <222> 384..391
- <223> matinspector prediction name MZF1\_01 score 0.986 sequence agaggga
- <221> protein\_bind
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- <223> matinspector prediction name SRY\_02 score 0.955 sequence gaaaacaaaaca
- <221> protein\_bind
- <222> 592..599
- <223> matinspector prediction name MZF1\_01

score 0.960 sequence gaagggga

<221> protein\_bind

<222> 618..627

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 name MYOD\_Q6
 score 0.981
 sequence agcatctgcc

<221> protein\_bind

<222> 632..642

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 score 0.958
 sequence tcccaccttcc

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 name S8\_01
 score 0.992
 sequence gaggcaattat

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<222> 335,376

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ctgggatgga aggcacggta

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 sequence ggactcacgtgctgct

<221> protein\_bind

<222> 193..204

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 score 0.965
 sequence actcacgtgctg

<221> protein\_bind

<222> 193..204

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 score 0.985
 sequence actcacgtgctg

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 score 0.985
 sequence cagcacgtgagt

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<222> 195..202

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       score 0.991
       sequence gcacgtga
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       score 0.968
       sequence catgggga
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       name ELK1 02
       score 0.963
       sequence ctctccggaagcct
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       score 0.974
       sequence tccggaagcc
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       score 0.963
       sequence agtgactgaac
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      name AP1FJ Q2
       score 0.961
       sequence agtgactgaac
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       score 1.000
       sequence tgtggtctc
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                                                                        60
aggacageat ttgtkacate tggtetactg cacetteect etgeegtgea ettggeettt
                                                                       120
kawaagctca gcaccggtgc ccatcacagg gccggcagca cacacatccc attactcaqa
                                                                       180
aggaactgac ggactcacgt gctgctccgt ccccatgagc tcagtggacc tgtctatqta
                                                                       240
gagcagtcag acagtgcctg ggatagagtg agagttcagc cagtaaatcc aagtgattqt
                                                                       300
catteetgte tgcattagta acteecaace tagatgtgaa aacttagtte ttteteatag
                                                                       360
gttgctctgc ccatggtccc actgcagacc caggcactct ccggaagcct ggaaatcacc
                                                                       420
cgtgtcttct gcctgctccc gctcacatcc cacacttgtg ttcagtcact gagttacaga
                                                                       480
ttttgcctcc tcaatttctc ttgtcttagt cccatcctct gttcccctgg ccagtttgtc
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tagctgtgtg gtctc

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              Met Pro Ser Tyr Lys Val Cys Gly Val Phe Cys Leu Phe
                          -20
                                               -15
gtt tgt ttg ttt ttg agc cag agt ttt gct ttt gtc ctc cag gct gga
                                                                        99
Val Cys Leu Phe Leu Ser Gln Ser Phe Ala Phe Val Leu Gln Ala Gly
                    - 5
gtg cag tgg cgc gat ctc tgc tca ctg caa cct cag ctt ccc agg ttc
                                                                       147
Val Gln Trp Arg Asp Leu Cys Ser Leu Gln Pro Gln Leu Pro Arg Phe
            10
                                15
ggg cca tcc tcc tgc ctc agc ctc cca agt ggc tgg gac tgc agg cgc
                                                                       195
Gly Pro Ser Ser Cys Leu Ser Leu Pro Ser Gly Trp Asp Cys Arg Arg
        25
                            30
cca cca ccc cgc ctg gct aat tct tgt gtt ttc ggt gga gac ggg gtt
                                                                       243
Pro Pro Pro Arg Leu Ala Asn Ser Cys Val Phe Gly Gly Asp Gly Val
    40
                        45
tca ccg gg
                                                                       251
Ser Pro
55
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<222> 35..274
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<222> 35..82
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                                                                       55
                                      Met Arg Leu Ser Leu Pro Leu
                                          -15
ctg ctg ctg ctg gga gcc tgg gcc atc cca ggg ggc ctc ggg gac
                                                                      103
Leu Leu Leu Leu Gly Ala Trp Ala Ile Pro Gly Gly Leu Gly Asp
agg gcg cca ctc aca gcc aca gcc cca caa ctg gat gat gag gag atg
                                                                      151
Arg Ala Pro Leu Thr Ala Thr Ala Pro Gln Leu Asp Asp Glu Glu Met
tac tea gee cac atg eec get cac etg ege tgt gat gee tge aga get
                                                                      199
Tyr Ser Ala His Met Pro Ala His Leu Arg Cys Asp Ala Cys Arg Ala
                       30
gtg gct tac cag gtg agt cct tca cca ctg tca cct gcc ctg ctc aca
                                                                      247
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Val Ala Tyr Gln Val Ser Pro Ser Pro Leu Ser Pro Ala Leu Leu Thr 45 50 ccc ctt ctc aag cca gcc ccc acc ggg 274 Pro Leu Leu Lys Pro Ala Pro Thr Gly 60 <210> 26 <211> 230 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 29..229 <221> sig\_peptide <222> 29..94 <223> Von Heijne matrix score 13.8000001907349 seg LGLLLLWLRGARC/GV aaggagtcag tctcagtcag gacacagc atg gac atg agg gtc ccc gct cag 52 Met Asp Met Arg Val Pro Ala Gln -20 ctc ctg ggg ctc ctg cta ctc tgg ctc cga ggt gcc aga tgt ggc gtc 100 Leu Leu Gly Leu Leu Leu Trp Leu Arg Gly Ala Arg Cys Gly Val -10 cag atg acc Cag ttt CCa Ctg tcc ctg tct gca tcg gta gga gac aga 148 Gln Met Thr Gln Phe Pro Leu Ser Leu Ser Ala Ser Val Gly Asp Arg 5 10 15 gtc acc atc act tgc cgg aca agc cat ata att aac atc ttt tta aat 196 Val Thr Ile Thr Cys Arg Thr Ser His Ile Ile Asn Ile Phe Leu Asn . 25 30 tgg tat cag cag aaa cca ggc aaa gcc cct tgg g 230 Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Trp 40 <210> 27 . <211> 195 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 44..193 <221> sig\_peptide <222> 44..112 <223> Von Heijne matrix score 13.8000001907349 seq VLLLLLLSGDVQS/SE agagggette eggggetgee ggtetgagtg cagagetget gte atg geg gee get 55 Met Ala Ala Ala 103 Leu Trp Gly Phe Phe Pro Val Leu Leu Leu Leu Leu Ser Gly Asp -15 -10 gtc cag agc tcg gag gtg ccc ggg gct gct gct gag gga tcg gga ggg 151 Val Gln Ser Ser Glu Val Pro Gly Ala Ala Ala Glu Gly Ser Gly Gly

22	
agt ggg gtc ggc ata gga gak cgc ttc aag att gag gga ctg gg Ser Gly Val Gly Ile Gly Xaa Arg Phe Lys Ile Glu Gly Leu 15 20 25	195
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agtcagtctc agacaggaca cagc atg gac atg agg gtc ccc gct cag ctc Met Asp Met Arg Val Pro Ala Gln Leu -20 -15	51
ctg ggg ctc Ctg cta ctc tgg ctc yka ggt gcc aga tgt gac atc cag Leu Gly Leu Leu Leu Trp Leu Xaa Gly Ala Arg Cys Asp Ile Gln -10 -5	99
atg aca cag tct cca gtc ctg cct gca tct gta gga gac aga gtc acc Met Thr Gln Ser Pro Val Leu Pro Ala Ser Val Gly Asp Arg Val Thr 5 10 15	147
atc act tgc cgg gca agt cag agc att ggc agc tat tta aac tgg tat  Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Tyr Leu Asn Trp Tyr  25 30 35	195
cag cat aaa cca ggg cat gcc cct cgc ctc ctg atc tat gct gca act Gln His Lys Pro Gly His Ala Pro Arg Leu Leu Ile Tyr Ala Ala Thr 40 45 50	243
act ttg tcg agg ggc ggs ccg gcc aga ttc agt Thr Leu Ser Arg Gly Gly Pro Ala Arg Phe Ser 55 60	276
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gcc gtg gtc ctg ctt tgt gcc tct gac ctg ctg ctg ctg ctg cta ctg Ala Val Val Leu Leu Cys Ala Ser Asp Leu Leu Leu Leu Leu Leu -20 -15 -10	99
cta cca ccg cct ggg tcc tgc gcc ggc cga agg tcg ccy dgg acg ccc Leu Pro Pro Pro Gly Ser Cys Ala Gly Arg Arg Ser Pro Xaa Thr Pro	147

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-5
gac gag tot acc cca cct ccc cgg aag aag aag gat att cgc gat
Asp Glu Ser Thr Pro Pro Pro Arg Lys Lys Lys Asp Ile Arg Asp
                     15
                                     . 20
tac aat gat gca gac atg gcg cgt ctt ctg gag caa ggg gag ggg
                                                                      240
Tyr Asn Asp Ala Asp Met Ala Arg Leu Leu Glu Gln Gly Glu Gly
<210> 30
<211> 461
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<221> CDS
<222> 80..460
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<223> Von Heijne matrix
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      seq WVLLLALLEGVQC/DV
<221> misc_feature
<222> 280..281,311..313
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                                                                       60
tgaacacaga ggactcacc atg gag ttg ggg ctg tgc tgg gtt ctc ctt tta
                                                                      112
                     Met Glu Leu Gly Leu Cys Trp Val Leu Leu Leu
gct ctt tta gaa ggt gtc caa tgt gac gtg gaa tta gtg gag tct ggg
                                                                      160
Ala Leu Leu Glu Gly Val Gln Cys Asp Val Glu Leu Val Glu Ser Gly
            -5
                                1
ggc ggc ttg gtg cag cct gga ggg tct ctg aga ctt tcc tgt gca gcc
                                                                      208
Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
                        15
                                            20
tct gga ttc aat ttt agc act tat gag atg cat tgg atc cgc cag gct
                                                                      256
Ser Gly Phe Asn Phe Ser Thr Tyr Glu Met His Trp Ile Arg Gln Ala
                    30
                                        35
cca ggg aag ggg ccg gag tgg gtn nca tat gtc agt ggt gga ggt gga
                                                                      304
Pro Gly Lys Gly Pro Glu Trp Val Xaa Tyr Val Ser Gly Gly Gly
                45
                                    50
acc agh nnn aac gcv sac tct gtg aag ggc cga ttc acc atc tcc aga
                                                                      352
Thr Xaa Xaa Asn Ala Xaa Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
                                65
gac aat gcc aac agt ttt gtg tat cta caa atg gac agt ctg cga gtc
                                                                      400
Asp Asn Ala Asn Ser Phe Val Tyr Leu Gln Met Asp Ser Leu Arg Val
                            80
gag gac acc gct ctc tat tac tgt gcg aga rgg gat tac gac ttc tgg
Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Arg Xaa Asp Tyr Asp Phe Trp
    90
agt ggt tat tat a
                                                                      461
Ser Gly Tyr Tyr
105
<210> 31
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<212> DNA
<213> Homo sapiens
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Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Asp Arg Thr Gly Gly

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90
                         95
                                           100
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                                                                       55
                                            Met Lys Leu Leu Trp
ttc ttc ctt ctc ctg ctg gca gct ccc aga tgg gtc ctg tcc cag gtg
                                                                      103
Phe Phe Leu Leu Leu Ala Ala Pro Arg Trp Val Leu Ser Gln Val
                -10
cag ctg gtg smg tcg ggc cca gga ctg gtg aag cct tcg ggg acc ctg
                                                                      151
Gln Leu Val Xaa Ser Gly Pro Gly Leu Val Lys Pro Ser Gly Thr Leu
                            10
tcc cta acg tgc act gts ksb ggk grs ksc ata act aat tac tac tgg
                                                                      199
Ser Leu Thr Cys Thr Val Xaa Gly Xaa Xaa Ile Thr Asn Tyr Tyr Trp
                        25
                                            30
agt bgg atc cgg cag tcc cca ggg aag gga ctg gag tgg att ggg act
                                                                      247
Ser Xaa Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Ile Gly Thr
                                        45
atc tac tac agt ggg agc gcc gac cac aac ccc tcc ctc agg agt mga
                                                                      295
Ile Tyr Tyr Ser Gly Ser Ala Asp His Asn Pro Ser Leu Arg Ser Arg
                55
                                    60
gcc act att tca tta gac acg cgc gg
                                                                      321
Ala Thr Ile Ser Leu Asp Thr Arg
            70
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<221> sig_peptide
<222> 49..108
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      seq LLXLLTALPPLWS/SS
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                                                                       57
ctg ggg ctg ctg ctc ctg ckc tta ctg aca gca ctg cca ccg ctg tgg
                                                                      105
Leu Gly Leu Leu Leu Xaa Leu Leu Thr Ala Leu Pro Pro Leu Trp
       -15
                            -10
tcc tcc tca ctg cct ggg ctg gac ack gct gaa agt aaa gcc acc akt
                                                                      153
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<222> 26..28

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Ser Ser Ser Leu Pro Gly Leu Asp Thr Ala Glu Ser Lys Ala Thr Xaa
                                       10
gca gac ctg atc ctg tct gcg ctg gag aga gcc acc ggg g
                                                                   193
Ala Asp Leu Ile Leu Ser Ala Leu Glu Arg Ala Thr Gly
<210> 35
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<212> DNA
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<220>
<221> CDS
<222> 151..438
<221> sig_peptide
<222> 151..234
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      seg LLLLLLPLRGQA/NT
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                                                                    60
120
aaaccgccca cctgcagttc cttctccggg atg gac gtg ggg ccc agc tcc ctg
                                                                   174
                               Met Asp Val Gly Pro Ser Ser Leu
                                           -25
ccc cac ctt ggg ctg aag ctg ctg ctc ctg ctg ctg ctc ctc
                                                                   222
Pro His Leu Gly Leu Lys Leu Leu Leu Leu Leu Leu Leu Pro Leu
                   -15
                                      -10
agg ggc caa gcc aac aca ggc tgc tac ggg atc cca ggg atg ccc ggc
                                                                   270
Arg Gly Gln Ala Asn Thr Gly Cys Tyr Gly Ile Pro Gly Met Pro Gly
ctg ccc ggg gca cca ggg aag gat ggg tac gac gga ctg ccg ggg ccc
                                                                   318
Leu Pro Gly Ala Pro Gly Lys Asp Gly Tyr Asp Gly Leu Pro Gly Pro
                          20
aag ggg gag cca gga atc cca gcc att ccc ggg atc cga gga ccc aaa
                                                                   366
Lys Gly Glu Pro Gly Ile Pro Ala Ile Pro Gly Ile Arg Gly Pro Lys
   30
                       35
ggg cag aag gga gaa ccc ggc tta ccc ggc cat cct ggg aaa aat ggc
                                                                   414
Gly Gln Lys Gly Glu Pro Gly Leu Pro Gly His Pro Gly Lys Asn Gly
                   50
                                      55
ccc atg gga ccc cct ggg atg cca
                                                                   438
Pro Met Gly Pro Pro Gly Met Pro
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     seq ILLLVAAATGTHA/QV
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Met Asp Cys Thr Trp Arg Ile Leu Leu Leu Val Ala Ala Ala Thr	Gly
-15 -10 -5	
acc cac gcc cag gtc cag ttg gta cag tct ggg cct gag gtg aaa	aag 154
Thr His Ala Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys	Lys
1 5 10	
cet ggg gee tea gtg aag gte tee tge eag gtt tee gga tac aac g	gtc 202
Pro Gly Ala Ser Val Lys Val Ser Cys Gln Val Ser Gly Tyr Asn 15 20 25	val
gtg gaa tta tcc atc cac tgg gtg cgt cag tcg cct gga aaa ggg (	att 350
Val Glu Leu Ser Ile His Trp Val Arg Gln Ser Pro Gly Lys Gly 1	
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gag tgg atg gga ggt ttt gac ctt gaa agt ggt gaa aca atc tac g	
Glu Trp Met Gly Gly Phe Asp Leu Glu Ser Gly Glu Thr Ile Tyr	
50 55 60	
cag agg ttc cag ggc aga atc acc atg acc gag gac tca tct tca c	gac 346
Gln Arg Phe Gln Gly Arg Ile Thr Met Thr Glu Asp Ser Ser Ser I	
65 70 75	•
aca gcc ttc atg gag ctg atc agc ctg aga cct gaa gat gcg gcc g	gtc 394
Thr Ala Phe Met Glu Leu Ile Ser Leu Arg Pro Glu Asp Ala Ala V	Val
80 85 90	
tac tac tgt gca acg atc cgg ctg cca gta gtg ctt ttt ttc gcg c	
Tyr Tyr Cys Ala Thr Ile Arg Leu Pro Val Val Leu Phe Phe Ala A	Ala
95 100 105	
tot ggg gcc agg gaa ccc tgg tcg ccg tct cct cag cmt cca cgg g	9 488
Ser Gly Ala Arg Glu Pro Trp Ser Pro Ser Pro Gln Xaa Pro Arg	
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Met Trp Leu Pro Leu Val Leu Leu I	_
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Ala Val Leu Leu Ala Val Leu Cys Lys Val Tyr Leu Gly Leu F	
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ctg ctg ctg ccg ctg ctg ctg ggc ctg aac gca gga gct gtc att gac Leu Leu Pro Leu Leu Gly Leu Asn Ala Gly Ala Val Ile Asp -10 -5 1	98
tgg ccc aca gag gag ggc aag gaa gta tgg gat tat gtg acg gtc cgc Trp Pro Thr Glu Glu Gly Lys Glu Val Trp Asp Tyr Val Thr Val Arg  10 15 20	146
aag gat gcc tac atg gg Lys Asp Ala Tyr Met 25	163
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-10 -5 1 act cag gag ccc ctc act gac tgt gtc ccc cgg ann aca gtc act ctc Thr Gln Glu Pro Leu Thr Asp Cys Val Pro Arg Xaa Thr Val Thr Leu 5 10 15 20	151
acc tgt ggc tcc agt att gga gct gtc acc aat ggt cat ttt ccc tac Thr Cys Gly Ser Ser Ile Gly Ala Val Thr Asn Gly His Phe Pro Tyr 25 30 35	199
tgg ttc caa cag aag cct ggc caa gcc ccc agg aca ctg att tct gat Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Thr Leu Ile Ser Asp 40 45 50	247
acg ttc aac aga cag tcc tcg aca cct gcc cgc ttc tct ggc tcc ctc Thr Phe Asn Arg Gln Ser Ser Thr Pro Ala Arg Phe Ser Gly Ser Leu  55 60 65	295
ota aga aga 222 agt ata ata aet ett tea agt aga 622 agt aga	242

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                                                                      391
 Glu Ala Glu Tyr Tyr Cys Val Leu Ser Tyr Ser Gly Gly Arg Pro Val
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                             -20
ctc tgc ctc cta ctg ggg cct ctt gca ggg gcc aag cct gtg cag g
                                                                       97
Leu Cys Leu Leu Gly Pro Leu Ala Gly Ala Lys Pro Val Gln
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atgsagcagg aaccgcggct gctggacaag aggggtgcgg tggatactga cctttgctcc
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ggcctcgtcg tgaagacaca gcgcatctcc ccgctgtagg cttcctccca cagaacccgt
                                                                      240
ttcgggcctc agagcgtctg gtgag atg ctg ttg ccg ctg ctg ctg cta
                                                                      292
                            Met Leu Leu Pro Leu Leu Leu Leu
                                            -10
ccc atg tgc tgg gcc gtg gag gtc aag agg ccc cgg ggc gtc tcc ctc
                                                                      340
Pro Met Cys Trp Ala Val Glu Val Lys Arg Pro Arg Gly Val Ser Leu
acc aat cat cac ttc tac gat gag tcc aag cct ttc acc tgc ctg gac
                                                                     388
Thr Asn His His Phe Tyr Asp Glu Ser Lys Pro Phe Thr Cys Leu Asp
           15
                                20
ggt tcg gcc acc atc cca ttt gat cag gtc aac gat gac tat tgc gac
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Gly Ser Ala Thr Ile Pro Phe Asp Gln Val Asn Asp Asp Tyr Cys Asp
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30
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tgc aaa gat ggc tct gac gag cca ggc acg gct gcc tgt cct aat ggc
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Cys Lys Asp Gly Ser Asp Glu Pro Gly Thr Ala Ala Cys Pro Asn Gly
                         50
ago tto cac tgc acc aac act ggc tat aag ccc ctg tat atc ccc tcc
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Ser Phe His Cys Thr Asn Thr Gly Tyr Lys Pro Leu Tyr Ile Pro Ser
aac c
                                                                       536
Asn
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                                                                       120
agggaactcg agagcarchy cc atg ggc aca cag gag ggc tgg wgc ctg ctg
                                                                       172
                         Met Gly Thr Gln Glu Gly Trp Xaa Leu Leu
                             -20
ctc tgc ctg gct cta tct gga gca gca gaa acc aag ccc cac cca gca
                                                                       220
Leu Cys Leu Ala Leu Ser Gly Ala Ala Glu Thr Lys Pro His Pro Ala
gag ggg cag tgg gga gtg gdc gtg gtc cta gac ygt ttc ctg gtg
                                                                      268
Glu Gly Gln Trp Arg Ala Val Xaa Val Val Leu Asp Xaa Phe Leu Val
                10
aag gac svt gcg cac cgt gga gct ctc gcc agc agt gag gac agg gca
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Lys Asp Xaa Ala His Arg Gly Ala Leu Ala Ser Ser Glu Asp Arg Ala
agg
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Arq
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Gln Ser Phe Ser Gly Val Ser Ser Arg Phe Ser Gly Ser Gly Ser Gly
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                                                                      120
cactcagaag cttggaccgc atcctagccg ccgactcaca caaggcagag ttgcc atg
                                                                      178
gag aaa att cca gtg tca gca ttc ttg ctc ctt gtg gcc ctc tcc tac
                                                                      226
Glu Lys Ile Pro Val Ser Ala Phe Leu Leu Val Ala Leu Ser Tyr
                -15
                                    -10
act ctg gcc aga gat acc aca gtc aaa cct gga gcc aaa aag gac aca
                                                                      274
Thr Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala Lys Lys Asp Thr
                            5
aag gac tot oga coo aaa otg coo cag aco oto too aga ggt tgg ggt
Lys Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser Arg Gly Trp Gly
                        20
gac caa ctc atc tgg act cag aca tat gaa gaa gct cta tat aaa tcc
                                                                      370
Asp Gln Leu Ile Trp Thr Gln Thr Tyr Glu Glu Ala Leu Tyr Lys Ser
                    35
                                        40
aag aca agc aac aaa ccc ttg atg att att cat cac ttg gat gag tgc
                                                                      418
Lys Thr Ser Asn Lys Pro Leu Met Ile Ile His His Leu Asp Glu Cys
                50
                                    55
cca cac agt caa gct tta aag aaa gtg ttt gct gaa aat aaa gaa atc
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Pro His Ser Gln Ala Leu Lys Lys Val Phe Ala Glu Asn Lys Glu Ile
                                70
cag aaa ttg gca gag cag ttt gtc ctc ctc aat ctg gtt tat gaa aca
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Gln Lys Leu Ala Glu Gln Phe Val Leu Leu Asn Leu Val Tyr Glu Thr
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act gac
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Ser Leu Ile Cys Gly Val Ser Gly Asp Ser Val Thr Ile Ser Gly Trp

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. 34 tgg agt tgg gtc cgc cag ccc cca ggg aag gga ctg gag tgg att tcg Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Ser 40 45 gaa atc gat cat ggt gga aac acc aat tac aac ccg tcc ctc aag agt 292 Glu Ile Asp His Gly Gly Asn Thr Asn Tyr Asn Pro Ser Leu Lys Ser 60 cga gtc kcc att tct tta gac aag tcc aag aat aag ttc tcc ctg agg 340 Arg Val Xaa Ile Ser Leu Asp Lys Ser Lys Asn Lys Phe Ser Leu Arg ctg acc tct gtg acc gcc gcg gac acc gcc atg tat kac tgt gcg aga 388 Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Met Tyr Xaa Cys Ala Arg 90 ggc ggt gcg bnc agc tcg tcc gct ttt gat gtc tgg ggc cta rgg aca 436 Gly Gly Ala Xaa Ser Ser Ser Ala Phe Asp Val Trp Gly Leu Xaa Thr 100 105 110 atg gtc atc atc tct tca gcc tc 459 Met Val Ile Ile Ser Ser Ala 115 <210> 48 <211> 437 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 20..436 <221> sig peptide <222> 20..76 <223> Von Heijne matrix score 11 seq TLLLLTVPSWVLS/QV <400> 48 gtgaatcetg etetecace atg gae ata ett tgt tee acg ete etg etm etg Met Asp Ile Leu Cys Ser Thr Leu Leu Leu -15 ack gtc ccg tcc tgg gtc tta tcc car gtc acc ttg arg gaa tct ggt 100 Thr Val Pro Ser Trp Val Leu Ser Gln Val Thr Leu Xaa Glu Ser Gly cct gcg ctg gtg aaa gcc aca cag acc ctc aga ctg acc tgc acc ttc 148 Pro Ala Leu Val Lys Ala Thr Gln Thr Leu Arg Leu Thr Cys Thr Phe 15 20 tct ggg ttc tca ctc agc act aat aga atg cgt gtg agt tgg atc cgt 196 Ser Gly Phe Ser Leu Ser Thr Asn Arg Met Arg Val Ser Trp Ile Arg 30 35 cag ccc cca 999 aag gcc ctg gag tgg ctt gca cgg att gat tgg gat 244 Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu Ala Arg Ile Asp Trp Asp 45 50 gat tat aag agg tac agc aca tot otg aag acc agg gto acc atc too 292 Asp Tyr Lys Arg Tyr Ser Thr Ser Leu Lys Thr Arg Val Thr Ile Ser 60 65 aag gac acg tcc aaa aac cag gtg atc ctg aca atg acc aac gtg gac 340 Lys Asp Thr Ser Lys Asn Gln Val Ile Leu Thr Met Thr Asn Val Asp 80 cct gcg gac aca gcc acc tat tac tqt qca cgc ctt tca acq qca qct 388 Pro Ala Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Leu Ser Thr Ala Ala 90 95 acc cca cag ttt ttt gac ttc tgg ggc cag gga gtc ctg gtc tcc gtc t 437

Thr Pro Gln Phe Phe Asp Phe Trp Gly Gln Gly Val Leu Val Ser Val

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110

105

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ctg cag gag tcg ggc cca gga ctg gtg aag cct tca cag acc ctg tcc Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln Thr Leu Ser 5 10 15	151
ctc acc tgc aca gtc tct ggt ggc tcc atc gac agt ggt aat tac tac Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asp Ser Gly Asn Tyr Tyr 20 25 30 35	199
tgg agc tgg atc cgg cag ccc gcc ggg aag gga ctg gag tgg att ggg Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu Trp Ile Gly 40 45 50	247
cgc atc tat agt act ggg agc acc aat tac aac ccc tcc ctc agc agt Arg Ile Tyr Ser Thr Gly Ser Thr Asn Tyr Asn Pro Ser Leu Ser Ser 55 60 65	295
cga gtc cag ata tcg tta gac acg tcc aag aac ctg ctc tcc ttg aac Arg Val Gln Ile Ser Leu Asp Thr Ser Lys Asn Leu Leu Ser Leu Asn 70 75 80	343
ctg acc tct gtg acc gcc gca gac acg gcc gtc tat ttt tgt gcg cga Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala Arg 85 90 95	391
acc ttc ccc ttc tac tgg tac ctc gat ctc tgg ggc cgt ggc atc ctg Thr Phe Pro Phe Tyr Trp Tyr Leu Asp Leu Trp Gly Arg Gly Ile Leu 100 115	439
gtc act gt Val Thr	447
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-10 -5 1 ctg cag gag tcg ggc cca aga ctg gtg aag cct tca cag acc ctg tcc	151

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									3	7							
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										agc Ser 30							199
										ggc Gly							247
Tyr	Ile	Tyr	Tyr 55	Asn	Trp	Ser	Thr	Tyr 60	Tyr	aat Asn	Pro	Ser	Leu 65	Arg	Ser		295
Arg	Val	Thr 70	Met	Ser	Met	Asp	Thr 75	Ser	Lys	aac Asn	Gln	Phe 80	Ser	Leu	Asn		343
Leu	Asn 85	Ser	Val	Thr	Ala	Ala 90	Asp	Thr	Xaa	atg Met	Tyr 95	Tyr	Cys	Ala	Arg		391
Gly 100	Arg	Gly	Arg	Leu	Gly 105	Trp	Phe	Xaa		tng Xaa 110							439
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Met	Lys	His	Leu	Trp -15	Phe	Phe	Leu	Leu	Leu -10	gtg Val	Āla	Ala	Pro	Arg	Trp		106
										ggc Gly							154
										gtc Val							202
										cgc Arg 40							250
ggc	_		Trp							act Thr		_			tac		298
										tcr Ser							346

	65		7	0				75			
aac cag ttc Asn Gln Phe 80	kcc ctg Xaa Leu	agc ctg Ser Leu	acc t Thr S 85	ct gtg er Val	act Thr	Val	gca Ala 90	qac	acg Thr	g	392
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gcc ctc tgc Ala Leu Cys	Cys Tyr (	Gln Ala	Asn Al 5	cc gag la Glu	Phe	Cys 1	Pro . 10	gct Ala	ctt Leu	Val	. 97
tct gag ctg Ser Glu Leu 15	tta gac ( Leu Asp )	Phe Phe	ttc at Phe I]	t agt le Ser	gaa Glu	cct of Property 25	ctg Leu	ttc Phe	aag Lys	tta Leu	145
agt ctt gcc Ser Leu Ala 30	Lys Phe A						•				172
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aaaaagtat gt	ttccttga	ctttcca	igcc k	stacag	gcc .	cacag	catt	c c	tgct	tgcag	180
cctatgtc ato	Ser Pro	gtc ctc Val Lev	ttg: Leu	gtg ct Val Le	g to	a ttg r Leu	tca Sei	a caa	a tg: n Cv:	c ctt s Leu	231
	-15			-10				-5	<b>-</b> ]		·
ctt tct gac o Leu Ser Asp I 1											259
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10

25

20

ctc acc tgc act gtc tct ggt gtc tcc agc agc aat tac gac tgg agt

Leu Thr Cys Thr Val Ser Gly Val Ser Ser Ser Asn Tyr Asp Trp Ser

200

35

tgg																	
Tr	g att	Arg	g cag g Gln	g gcc Ala 40	cca Pro	ggg Gly	aag Lys	gga Gly	ctg Leu 45	gaa Glu	tgg Trp	att Ile	G1y	tat Tyr 50	ata Ile	248	ł
gac Asp	gat Asp	agt Sei	aag Lys 55	aat Asr	aga Arg	ggg Gly	agt Ser	acg Thr	Thr	tac Tyr	aac Asn	ccc Pro	tcc Ser 65	ctc	aag Lys '	296	;
agt Ser	cga Arg	gto Val	acc Thr	ata Ile	tcg Ser	stg Xaa	gac Asp 75	acg	tcc Ser	aag Lys	ast Xaa	cag Gln 80	ttq	tcc	ctg <b>Le</b> u	344	
agg	ctg Leu 85	acc Thr	tct Ser	gtg Val	acc	kcs Xaa 90	gca	gac Asp	acg Thr	gcc Ala	gtc Val 95	tat	tat Tyr	tgt Cys	gcg Ala	392	!
aga Arg 100	Lys	tca Ser	tct Ser	atg Met	cat His	agt Ser	agt Ser	ggc Gly	tgg Trp	cat His 110	aac	cgg Arg	agt Ser	ctc Leu	tac Tyr 115	440	,
			gat Asp					٠							113	457	J
<21	0 > 5 1 > 4	20							•				•		* - I		
	2> D 3> H		sapi	ens	•												
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						25				- 2					-15		
Phe	Phe	CCC		CTO	gtg	qca	act							cag		100	
		Leú	Leu	Leu -10	Val	Ala	Ala	Pro	-5	Trp	Val	Leu	Ser	Gln 1	Val	. 100	
ctg	cag	Leu	Leu	Leu -10 ggc	Val cca	Ala gga Gly	Ala	Pro gtg	Arg -5 aag	Trp	Val tcg	Leu	Ser	Gln 1 ctq	Val .	148	
ctg Leu ctc	cag Gln acc	Leú gag Glu 5 tgc	tcg Ser gct	Leu -10 ggc Gly gtc	Val cca Pro	Ala gga Gly	Ala ctg Leu 10 ggc	Pro gtg Val tcc	Arg -5 aag Lys atc	Trp cct Pro	Val tcg Ser	ggg Gly 15	ser acc Thr	Gln 1 ctg Leu	tcc Ser		
ctg Leu ctc Leu agt Ser 35	cag Gln acc Thr 20 tgg	gag Glu 5 tgc Cys gtc Val	tcg Ser gct Ala cgc	Leu -10 ggc Gly gtc Val cag Gln	val cca Pro tct Ser acc Thr	Ala gga Gly ggt Gly 25 cca Pro	Ala ctg Leu 10 ggc Gly ggg	Pro gtg Val tcc Ser aag Lys	Arg -5 aag Lys atc Ile 999 Gly	Trp cct Pro ata Ile ctg Leu 45	tcg Ser agt Ser 30 gag Glu	Ggg Gly 15 agt Ser tgg Trp	Ser acc Thr aat Asn att Ile	Gln 1 ctg Leu tgg Trp ggg Gly	tcc ser tgg Trp gaa Glu 50	148	
ctg Leu ctc Leu agt ser 35 atc Ile	cag Gln acc Thr 20 tgg Trp tat Tyr	gag Glu 5 tgc Cys gtc Val gaa Glu	tcg Ser gct Ala cgc Arg	Leu -10 ggc Gly gtc Val cag Gln ggg Gly 55	cca Pro tct Ser acc Thr 40 atc	Ala gga Gly ggt Gly 25 cca Pro acc	Ala ctg Leu 10 ggc Gly ggg Gly aac Asn	Pro gtg Val tcc Ser aag Lys tac Tyr	Arg -5 aag Lys atc Ile 999 Gly aac Asn 60	Trp cct Pro ata Ile ctg Leu 45 ccg Pro	tcg Ser agt Ser 30 gag Glu tcc Ser	Leu 999 Gly 15 agt Ser tgg Trp ctc Leu	Ser acc Thr aat Asn att Ile aag Lys	Gln 1 ctg Leu tgg Trp ggg Gly agt Ser 65	tcc Ser tgg Trp gaa Glu 50 cga Arg	148	
ctg Leu ctc Leu agt Ser 35 atc Ile gtc Val	cag Gln acc Thr 20 tgg Trp tat Tyr	gag Glu 5 tgc Cys gtc Val gaa Glu att Ile	tcg Ser gct Ala cgc Arg gat Asp tca Ser 70	Leu -10 ggc Gly gtc Val cag Gln ggg Gly 55 gtg Val	cca Pro tct Ser acc Thr 40 atc Ile	gga Gly ggt Gly 25 cca Pro acc Thr	ctg Leu 10 ggc Gly ggg Gly aac Asn	Pro gtg Val tcc Ser aag Lys tac Tyr aag Lys 75	Arg -5 aag Lys atc Ile 999 Gly aac Asn 60 aac Asn	Trp  cct Pro  ata Ile  ctg Leu 45 ccg Pro  cag Gln	Val tcg Ser agt Ser 30 gag Glu tcc Ser ttc	Leu  999 Gly 15 agt Ser  tgg Trp  ctc Leu tcc Ser	Ser acc Thr aat Asn att Ile aag Lys ctg Leu 80	Gln 1 ctg Leu tgg Trp ggg Gly agt Ser 65 aag Lys	tcc Ser tgg Trp gaa Glu 50 cga Arg atg Met	148 196 244	
ctg Leu ctc Leu agt Ser 35 atc Ile gtc Val agg Arg	cag Gln acc Thr 20 tgg Trp tat Tyr atc Ile tct Ser	gag Glu 5 tgc Cys gtc Val gaa Glu att Ile gtg Val 85	tcg Ser gct Ala cgc Arg gat Asp tca Ser 70 acc Thr	Leu -10 ggc Gly gtc Val cag Gln ggg Gly 55 gtg Val gcc Ala	cca Pro tct Ser acc Thr 40 atc Ile gac Asp	gga Gly ggt Gly 25 cca Pro acc Thr aag Lys	Ala ctg Leu 10 ggc Gly ggg Asn acc Ala acg Thr	Pro gtg Val tcc Ser aag Lys tac Tyr aag Lys 75 gcc Ala	Arg -5 aag Lys atc Ile 999 Gly aac Asn 60 aac Asn gtc Val	Trp  cct Pro  ata Ile  ctg Leu 45 ccg Pro  cag Gln  tat Tyr	Val tcg Ser agt Ser 30 gag Glu tcc Ser ttc Phe	Leu  999 Gly 15 agt Ser  tgg Trp  ctc Leu  tcc Ser  tgt	Ser acc Thr aat Asn att Ile aag Lys ctg Leu 80 gcg	Gln 1 ctg Leu tgg Trp ggg Gly agt Ser 65 aag Lys	tcc Ser tgg Trp gaa Glu 50 cga Arg atg Met	148 196 244 292	

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10

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-15 -10	-5
tcc cag gtc cag ctt gtg cag tct ggg gct gag	
Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu	Val Lvs Lvs Pro Glv
1 5 10	15
gcc tca gtg aag gtt tcc tgc aag gct tct gga	tac ayc ttc act ary 201
Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly	Tyr Xaa Phe Thr Xaa
20 25	30
tmt get atn cat tgg gtg cgc cag gcc ccc gga	car agr ctt gag tgg 249
Xaa Ala Xaa His Trp Val Arg Gln Ala Pro Gly	<del>-</del>
35 40	45
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50 55	60
tte cag gre aga gte acc wtt acc agg gae aca	
Phe Gln Xaa Arg Val Thr Xaa Thr Arg Asp Thr	Ser Ala Ser Thr Val
65 70	75
tcc atg gag ctg agc agc ctg aga tct gaa gac	acg gct gtg tat ttc 393
Ser Met Glu Leu Ser Ser Leu Arg Ser Glu Asp	Thr Ala Val Tyr Phe
80 85 90	95
tgt gcg aga gat tgg gaa att gca gta gta cca	
Cys Ala Arg Asp Trp Glu Ile Ala Val Val Pro 100 105	
tac ggg ttc gac cct ggg gcc agg gaa cct	110 471
Tyr Gly Phe Asp Pro Gly Ala Arg Glu Pro	. 4/1
115 120	
•	•
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ggggtaaaat gaggatcctt cccacaaac attgctatta	
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atccaaagaa ga atg gag gcc aga gtg gag cgt gc	
Met Glu Ala Arg Val Glu Arg Al	
-25 -20	-15
gtc tta ttt ctt tgt gta ttt ctg gga atg tct	tgg gct ggc gcc gaa 279
Val Leu Phe Leu Cys Val Phe Leu Gly Met Ser	
-10 -5	1
ccg ctt cgg tat ttt gtg gcg gag gaa acc gag	aga ggc acc tdk ctt 327
Pro Leu Arg Tyr Phe Val Ala Glu Glu Thr Glu	Arg Gry Thr Xaa Leu

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<223> Von Heijne matrix

score 10.8000001907349

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Trp Phe Phe Leu Leu Val Ala Ala Pro Arg Trp Val Leu Ser Gln	98
-15 -10 -5 1	
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Glu Gln Leu Arg Gln Trp Gly Ala Xaa Leu Leu Lys Pro Ser Glu Thr	
5 10 15	
ctg tcc ctc acc tgt agt gtc tat ggt ggg tcc ttc aat ggt tac tac	194
Leu Ser Leu Thr Cys Ser Val Tyr Gly Gly Ser Phe Asn Gly Tyr Tyr	
20 25 30	
tgg agc tgg atc cgc cag tcc cca ggg aag ggg ctg gag tgg att ggg Trp Ser Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Ile Gly	242
35 40 45	
gga atc aat cac agc gga agc acc ctc tcc aac ccg tcc ctc aag agt	290
Gly Ile Asn His Ser Gly Ser Thr Leu Ser Asn Pro Ser Leu Lys Ser	
50 55 60 65	
cgc gtc gac ctc tca gtt gat gcg tcc aag gac cag gtg tcc ctg agg	338
Arg Val Asp Leu Ser Val Asp Ala Ser Lys Asp Gln Val Ser Leu Arg	٠
70 75 80	
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85 90 95	
ccc cat tac gat atg tcg act gat tct tcg ttt gac ggt ttt gat ctc	434
Pro His Tyr Asp Met Ser Thr Asp Ser Ser Phe Asp Gly Phe Asp Leu	
100 105 110	
tgg gg	439
Trp	
-210. 62	
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Met Met Leu Leu Ala Leu Phe Phe Leu Leu	
-15 -10	
agg att gct ttg gct agt caa ggt ctt ttg tgg ttc cat aca aat ttt Arg Ile Ala Leu Ala Ser Gln Gly Leu Leu Trp Phe His Thr Asn Phe	159
-5 1 5 10	
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Lys Val Phe Val Val Ser Ile Cys Val Lys Thr Ile Ile Gly Ile Ser	_0,
15 20 25	
ggg ggc a	
<del>-</del>	214
Gly Gly	214

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45 <211> 297 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 63..296 <221> sig\_peptide <222> 63..119 <223> Von Heijne matrix score 10.6999998092651 seq ILFLVAAATGALS/QV <400> 64 gtgcatcacc cagcaaccac atctgtcctc tagagaatcc cctgagadht ccgttcctca cc atg gac tgg acc tgg agg atc ctc ttc ttg gtg gca gcr gcc aca 107 Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr -15 -10 qqa qcc ctc tcc cag gtg cag ctg gtr cag tct gga ggt gar gtg aag 155 Gly Ala Leu Ser Gln Val Gln Leu Val Gln Ser Gly Gly Glu Val Lys aag oot ggg goo toa gtg agg gto too tgc aag goo tot gga tac agc 203 Lys Pro Gly Ala Ser Val Arg Val Ser Cys Lys Ala Ser Gly Tyr Ser 15 20 ttc atc ggc tat tat gta cac tgg ata cga cag act cct ggg cga sgc 251 Phe Ile Gly Tyr Tyr Val His Trp Ile Arg Gln Thr Pro Gly Arg Xaa 35 297 ctt gag tgg atg ggg tgg gtc aac cct crs act ggc gac aac ggg g Leu Glu Trp Met Gly Trp Val Asn Pro Xaa Thr Gly Asp Asn Gly 45 <210> 65 <211> 370 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 237..368 <221> sig\_peptide <222> 237..347 <223> Von Heijne matrix score 10.6000003814697 seg YLLLVLSLSLSLC/CS aaaqqtacac aattgaaaaa aattgtatcc ttcacaacag atgtgggcag tcaactttta 60 gaccttgtgt Ctttagtttg acctgtcctt cagtgagtgt atataaaatt ctaagctaaa 120 acatattttc tgaaattgtg aaggtattgc atgtctatct tcttgcctac tctaaatata 180 tcaatcgttt tcttgggaag ttagtctttc tttcacactt gtctgtagat ctttac atg 239 ttc ttt cag ttt tgg aag tcc tct gca tat tta ata ttt gtt agt att 287 Phe Phe Gln Phe Trp Lys Ser Ser Ala Tyr Leu Ile Phe Val Ser Ile tot aaa ogt tit cit cct gic tac ctc cit git ctc tct ctc 335 Cys Lys Gly Phe Leu Pro Val Tyr Leu Leu Val Leu Ser Leu Ser -20 ctc tct ctc tgt tgc tct ctc ttg ctc tct ctc ca 370 Leu Ser Leu Cys Cys Ser Leu Leu Leu Ser Leu

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                                                                      104
Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly Val His Ser Gln
                    -10
                                         - 5
gtc cac ctt gtt cag tct ggg gct gar gtg aag aag cct ggg act ccg
                                                                      152
Val His Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Thr Pro
gtg aac att too tgt aag got tit ggo tac acc tto cot goo tit got
                                                                      200
Val Asn Ile Ser Cys Lys Ala Phe Gly Tyr Thr Phe Pro Ala Phe Ala
                            25
ata cat tgg gtt cgc cag gcc ccc gga caa agt ctt gag tgg atg gga
                                                                      248
Ile His Trp Val Arg Gln Ala Pro Gly Gln Ser Leu Glu Trp Met Gly
                        40
                                             45
tgg gtc aac att ggc cat ggc aac aca aag tat tca cag aag ttt cag
                                                                      296
Trp Val Asn Ile Gly His Gly Asn Thr Lys Tyr Ser Gln Lys Phe Gln
                    55
                                        60
ggc aga etc gec atc tec aga gac acg tec geg aac ata gte tac nng
                                                                      344
Gly Arg Leu Ala Ile Ser Arg Asp Thr Ser Ala Asn Ile Val Tyr Xaa
                                    75
gaa ctg agc ggc ctg aga tct gaa gac acg gct gtc tat tac tgt gcg
                                                                      392
Glu Leu Ser Gly Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
           .85
                                90
agg gat aat ctt ttc ttt ggc agt atg ggc ttt gac
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Arg Asp Asn Leu Phe Phe Gly Ser Met Gly Phe Asp
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ctc Leu -10	ctc Leu	ggc Gly	ctc Leu	ctc Leu	tct Ser -5	cac His	tgc Cys	aca Thr	ggc Gly	tct Ser 1	gtg Val	acc Thr	tcc Ser	tat Tyr 5	gtg Val		103
ctg Leu	act Thr	cag Gln	cct Pro 10	ccc Pro	tcg Ser	gtg Val	tca Ser	gtg Val 15	gcc Ala	cca Pro	gga Gly	aag Lys	acg Thr 20	gcc Ala	agc Ser		151
att Ile	acc Thr	tgt Cys 25	999 Gly	gga Gly	gac Asp	aac Asn	att Ile 30	gaa Glu	agt Ser	caa Gln	gtt Val	gta Val 35	cac His	tgg Trp	cac		199
cag Gln	cag Gln 40	aag Lys	cca Pro	ggg Gly	cag Ġln	gcc Ala 45	cct Pro	ata Ile	ttg Leu	gtc Val	atc Ile 50	tat Tyr	gat Asp	gat Asp	acc Thr		247
gac Asp 55	cgg Arg	ccc Pro	tca Ser	Gly	atc Ile 60	cct Pro	gac Asp	cga Arg	ttc Phe	tct Ser 65	ggc Gly	tcc Ser	aac Asn	tct Ser	999 Gly 70		295
His	Thr	Ala	Thr	Leu 75	Thr		Ser	Arg	Val 80	Glu	Ala	Gly	Asp	Glu 85	Ala		343
gac Asp	tat Tyr	tat Tyr	tgt Cys 90	cag Gln	gtg Val	tgg Trp	gat Asp	aga Arg 95	agt Ser	agt Ser	ggt Gly	cag Gln	gga Gly 100	ata Ile	ttc Phe		391
Gly	Gly	Gly 105	Thr	Lys	Leu	acc Thr	Val 110	Leu	Arg	Gln	Pro	Lys 115	Ala	Ala	Pro	-	439
tcg Ser	gtc Val 120	act Thr	ctg Leu	ttc Phe	ccg Pro	ccc Pro 125	tcc Ser	tct Ser	gag Glu	gag Glu	ctt Leu 130	caa Gln	gcc Ala	aac Asn	aag Lys		487
gcc Ala 135				,								*				•	493
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	> DN > Ho		apie	ns								•		,		٠.	
	> CD > 36		9														•
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		n He ore	ijne	0000	0381	4697				•							
	> 68	•								<b>.</b>							
tggc	agtt	ac c	ccag	CLCC	c aa	atat	agat	acc	M	let A 15			_	he L	_		53
			Val			tcg Ser											101
ctg Leu	Glu	tgc Cys 10	agt ( Ser	ggt Gly I	atg Met	atc Ile	atg Met 15	gct Ala	tac Tyr	tgc Cys	agc Ser	atc Ile 20	agc Ser	ctc Leu	cca Pro		149
					Leu	acc Thr . 30				a							180

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                                    Met Lys His Leu Trp Phe
                                                          -15
 tte etc etc etg gtg tea get eec aga tgg gte etg tet eag gtg eag
                                                                       103
 Phe Leu Leu Val Ser Ala Pro Arg Trp Val Leu Ser Gln Val Gln
             -10
                                 -5
 cta cag gag tcg ggc cca gga ctg gtg aag cct tcg ggg agg ctg tcc
                                                                       151
 Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly Arg Leu Ser
                         10
                                             15
 ctc gcc tgc gat gtg gtg gaa ttg agt ccg ccg gcc ccc agg ggc ggg
                                                                       199
 Leu Ala Cys Asp Val Val Glu Leu Ser Pro Pro Ala Pro Arg Gly Gly
 20
                     25
                                         30
 tot goa gtg cat ctc aga aat ctt toa toa tgg gag ccc cac cta caa
                                                                       247
 Ser Ala Val His Leu Arg Asn Leu Ser Ser Trp Glu Pro His Leu Gln
                                     45
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 ccc gtc tcg ggg
                                                                       259
 Pro Val Ser Gly
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                                                                        48
        Met Thr Tyr Phe Pro Leu Gly Arg Tyr Pro Val Met Gly Leu
                -30
                                    -25
                                                        -20
 ctg gat caa atg gta gtt gtg ttt tta ctt ctt tta gtc tcc aca ctt
                                                                        96
 Leu Asp Gln Met Val Val Val Phe Leu Leu Leu Leu Val Ser Thr Leu
                                 -10
 tot too gta gtg gtt tta cta gtt tgc att ccc acc agc agt gta aaa
                                                                       144
 Ser Ser Val Val Leu Leu Val Cys Ile Pro Thr Ser Ser Val Lys
                                             10
 ttq ttc cct ttt cac cat atc cac acc aac tgg g
                                                                       178
 Leu Phe Pro Phe His His Ile His Thr Asn Trp
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                                                                        54
                                            Met Glu Phe Gly Leu
age tgg gtt etc etc gtt get atg tta aga ggt etc eag tgt eaa gtg
                                                                       102
Ser Trp Val Leu Leu Val Ala Met Leu Arg Gly Leu Gln Cys Gln Val
                -10
cag ctg gtg gag tct ggg gga acc gcg gg
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Gln Leu Val Glu Ser Gly Gly Thr Ala
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                                                    Met Tyr Leu
                                                    -15
age ttg tta att cta ctt ttg gaa aat gtc agt ggc ttt ccc ttt cct
                                                                       103
Ser Leu Leu Leu Leu Leu Glu Asn Val Ser Gly Phe Pro Phe Pro
cta att ttc cag ctt cat gca tcc cct ggc cat aag ata ctt cca gac
                                                                       151
Leu Ile Phe Gln Leu His Ala Ser Pro Gly His Lys Ile Leu Pro Asp
                    10
tgt atg ata tat tct atc act gtc agc ctt atg ttc cct gtg gtt gac
                                                                       199
Cys Met Ile Tyr Ser Ile Thr Val Ser Leu Met Phe Pro Val Val Asp
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                                    30
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tat ata agc acg caa ggg
                                                                       217
Tyr Ile Ser Thr Gln Gly
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tat ttg gct atc ttg ttc tgc ctc tct ctc tcc tta tgg ttc tdk tgt Tyr Leu Ala Ile Leu Phe Cys Leu Ser Leu Ser Leu Trp Phe Xaa Cys -20 -15 -10	162
tta ctt ttt ttg ctt ttt gct tgg cct ggg Leu Leu Phe Leu Leu Phe Ala Trp Pro Gly -5	192
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Met Ala Trp Thr Pro Leu Leu Phe Leu Thr -20 -15	
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-10 -5 1 5	
tog occ tot goo tot goo too otg gga goo tog gto aag oto acc tgo Ser Pro Ser Ala Ser Ala Ser Leu Gly Ala Ser Val Lys Leu Thr Cys	148
10 15 20	
act ctg agc agt ggg cac agc aac tac ggc atc gct tgg tat cag cag	196
Thr Leu Ser Ser Gly His Ser Asn Tyr Gly Ile Ala Trp Tyr Gln Gln 25 30 35	
cag cca gag aag ggc cct cga ttc ttg atg aaa gtt aac agt gat ggc	244
Gln Pro Glu Lys Gly Pro Arg Phe Leu Met Lys Val Asn Ser Asp Gly 40 45 50	
age cae atg aag geg gae ggg ate eet gat ege tte tea gge tee age	292
Ser His Met Lys Ala Asp Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser  55 60 65 70	
tot ggg got gag ogo tac oto too ato too ago oto a	329
Ser Gly Ala Glu Arg Tyr Leu Ser Ile Ser Ser Leu 75	

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taacatttat tgaagagact ggcctttccc caatgagtgt tcttggcacc tttgtcaaaa
                                                                      120
gtcagttggc cgtagatatg tggattaatt tctgtgttcc ctgttttgtt ccattggcct
                                                                      180
atgtgtctgt ttttatgaca gtaccaggtt gttttggtta ctacagcttt gtagtttact
                                                                      240
ttgaggtetg ttagtgtg atg cet eta get ttg tte ttt ttg ete agt gtt !
                                                                      291
                    Met Pro Leu Ala Leu Phe Phe Leu Leu Ser Val
                                    -10
gct ttg gct att cag ggt cag gg
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Ala Leu Ala Ile Gln Gly Gln
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                                                                       58
atg gac tgg acc tgg agg rwc ttc tgc ttg ctg gct gta gct cca ggt
                                                                      106
Met Asp Trp Thr Trp Arg Xaa Phe Cys Leu Leu Ala Val Ala Pro Gly
                -15
get cae tee cag gtg cag etg gtg cag tet ggg get gag gtg aag aag
                                                                      154
Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
           1
cct ggg gcc tca gtg aag gtt tcc tgc aag gca tct gga tac acc ttc
                                                                      202
pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
acc agc cac tat atg cac tgg gtg cga cag gcc cct gga caa ggg ctt
                                                                      250
Thr Ser His Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
                    35
                                       . 40
gag tgg atg gga ata atc tac cct gat agt gat acc act aag tac cba
                                                                      298
Glu Trp Met Gly Ile Ile Tyr Pro Asp Ser Asp Thr Thr Lys Tyr Xaa
                                   55
cag aac ttc cag ggc aga gtc acc atg act agg gac acg tcc acg agc
                                                                      346
Gln Asn Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
                                70
aca gtc tac atg gag ctg agc ctg aca tct gac gac acg gcc gtg
                                                                      394
Thr Val Tyr Met Glu Leu Ser Ser Leu Thr Ser Asp Asp Thr Ala Val
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seq XLXLSVLLGXXXX/KX

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tat tat tgt gct aga gag gcg tat agt ggg agc tac cgc ttt gac tac
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Tyr Tyr Cys Ala Arg Glu Ala Tyr Ser Gly Ser Tyr Arg Phe Asp Tyr
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tgg gg
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Trp
110
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                 Met Asp Leu Met Cys Lys Lys Met Arg His Leu Trp
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                                          -20
                                                              -15
tto etc etc etg etg gtg geg get ecc aga tgg gte etg tec eag etg
                                                                       99
Phe Leu Leu Leu Val Ala Ala Pro Arg Trp Val Leu Ser Gln Leu
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cag ctt cag gag tcg ggc cca gga ctg gtg aag gct tcg gag acc ctg
Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Ala Ser Glu Thr Leu
                            10
tcc ctc gcc tgc agt gtc tct ggt gac tcc atc agc agt ggt aat tat
                                                                      195
Ser Leu Ala Cys Ser Val Ser Gly Asp Ser Ile Ser Ser Gly Asn Tyr
                        25
tac tgg ggc tgg atc cgg cag ccc cca ggg aag gga ctg cag tgg ctt
                                                                      243
Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Gln Trp Leu
                                        45
ggg agt ctt tgg aat cgt ggc ggt ccg caa tac aay hcc tcc ctc aag
                                                                      291
Gly Ser Leu Trp Asn Arg Gly Gly Pro Gln Tyr Asn Xaa Ser Leu Lys
aat cga gtc acc gtg tcc gta gac acg tcc acg aat cat ttc ttt ctg
                                                                      339
Asn Arg Val Thr Val Ser Val Asp Thr Ser Thr Asn His Phe Leu
aga ctg aat tcc gtg aay vgh gga cac ggc aat tta tta ctg tgc gcg a
                                                                      388
Arg Leu Asn Ser Val Asn Xaa Gly His Gly Asn Leu Leu Cys Ala
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ctg ttr ggg sck rts tbt kgc aag gmg gac ttt gtg ggg cat cag gtg Leu Leu Gly Xaa Xaa Xaa Xaa Lys Xaa Asp Phe Val Gly His Gln Val	. 99
ctc cga atc tct gta gcc gat g Leu Arg Ile Ser Val Ala Asp 10 15	121
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tgaacagaga gaactcacc atg gag ctt ggg ctg agc tgg ctt ttt ctt gtg  Met Glu Leu Gly Leu Ser Trp Leu Phe Leu Val  -15 -10	112
gct ttt tta aaa ggt gtc cag tgt gag gtg cag ttg ttg gag tct ggg Ala Phe Leu Lys Gly Val Gln Cys Glu Val Gln Leu Leu Glu Ser Gly -5	160
gga ggc ttg gtc cag cct ggg ggg tcc ctg aga ctc tca tgt gca gcc	208

seq LLLLQALPSPLSA/RA

	10					15					20						
Ser	gga Gly	ttc Phe	acc Thr	ttt Phe	agc Ser 30	tcc Ser	tat Tyr	gcc Ala	atg Met	Leu	tgg Trp	gtc Val	cgc Arg	cag Gln	Ala	•	256
25	aat	220	aaa	cta		taa	ata	+00	aat	35	205				40		204
Pro	Gly	aag Lys	Gly	Leu 45	Glu	Trp	Val	Ser	Gly 50	Ile	Ser	Ala	Gly	Ala 55	Asp		304
gat	aca	tat	gat	gca	gac	tcc	gtg	aag		cqq	ttc	acc	att		aga		352
Asp	Thr	Tyr	Asp 60	Ala	Asp	Ser	Val	Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Arg		
gac Asp	gat Asp	tcc Ser	aag Lys	aaa Lys	atc Ile	cta Leu	tat Tyr	cta Leu	caa Gln	atg Met	aac Asn	agc Ser	ctg Leu	aga Arq	gcc Ala		400
		75					80					85		_			
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<400 gaac cgc Arg gca	sc se > 81 :aatt ctg Leu gac	ta tata	GLLV ctgc gtt Val	LFLT acga gtc Val cca	CYA/ a ta ctg Leu gac	DD cccc gga Gly aag	ctg ctg Leu -10 cca	ctt Leu gac	gtc Val gac	Met tta Leu aag	ttc Phe cca	ctg Leu -5 gac	Ser -20 acc Thr	tgc Cys	tat Tyr ggc		٠
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<213> Homo sapiens

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Met Glu Arg Arg Leu Leu Gly Gly Met Ala -20 -15	
ctc ctg ctc ctc cag gcg ctg ccc agc ccc ttg tca gcc agg gct gaa	161
Leu Leu Leu Gln Ala Leu Pro Ser Pro Leu Ser Ala Arg Ala Glu -10 -5 1	
ccc ccg cag gat aag gaa gcc tgt gtg ggt acc aac aat caa agc tac	209
Pro Pro Gln Asp Lys Glu Ala Cys Val Gly Thr Asn Asn Gln Ser Tyr 5 10 15	
atc tgt gac aca gga cac tgc tgt gga cag tct cag tgc tgy aac tac	257
Ile Cys Asp Thr Gly His Cys Cys Gly Gln Ser Gln Cys Cys Asn Tyr	
20 25 30 35	. 205
tac tat gaa ctc tgg tgg ttc tgg ctg gtg tgg acc atc atc atc Tyr Tyr Glu Leu Trp Trp Phe Trp Leu Val Trp Thr Ile Ile Ile	305
40 45 50	
ctg age tgc tgt tgt tgc cac cac cgc cga gcc aag cac cgc ctt	353
Leu Ser Cys Cys Val Cys His His Arg Arg Ala Lys His Arg Leu ( 55 60 65	
cag gcc cag cag cgg caa cat gaa atc aac ctg atc gct tac cga g	399
Gln Ala Gln Gln Arg Gln His Glu Ile Asn Leu Ile Ala Tyr Arg 70 75 80	•
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atcacttctt ggtaacaatg caagacctca taaacctaaa gaagagaaag aaaagaaaac	180
ttttgttact ttvctttttt gcttgtcact tatatacagg ctatgtgaga atataatttg	240
taggtataac acattaagaa aaagttatct tcattggata gaattga atg gtg gtc	296
Met Val Val -25	
gct gat agg aat agg gcg tcc tct agc tct tat ctc tgt ctc tta ctc	344
Ala Asp Arg Asn Arg Ala Ser Ser Ser Tyr Leu Cys Leu Leu	• • • • • • • • • • • • • • • • • • • •
-20 -15 -10	
ttt tct ctt tct ctt ttt ctc tgt cat gag act gtg tgt gac agg gcc	392
Phe Ser Leu Ser Leu Phe Leu Cys His Glu Thr Val Cys Asp Arg Ala	
-5 1 5 acc tgt	398
Thr Cys	,
10	
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NULLY MOVES	

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220	200	-35	acc	aag	acc	222	-30		tta	tet	ctg	-25	tca	+++	art.	,	149
Asn .											Leu -10						149
_	_										tgt						197
-5	•				1				5		Cys			10			
											999						245
			15					20			Gly	-	25		Asp		
Met .		Asp					Ala				tgc Cys	Thr			٠		290
		30					35	,				40				•	
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	se	eq II	ıt I V t	LTITIAL	зько,	/ KA											
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	atct	gt t	_			-			-	gcw	atg a	aa t	ca t	tc a	gc	ıc	60 114
ccag	atct gaca	gt t	gago	agct	a ta	aggtä	atct	g cca	agra	gcw a	atg a Met I	aa t ys S	ca t Ser I	tc a	igc Ser -15	ac	
ccag cttg	atct gaca	gt ticc a	ttc	agct	a ta gtc	aggta	ctc	g cca	gcc	ggc 1	atg a Met I ctg	aa t ys S agg	ca t Ser I	tc a Phe s aag	gc Ser 15 gcc	ıc	
ccag	atct gaca	gt ticc a	ttc	agct	a ta gtc	aggta	ctc	g cca	gcc	ggc 1	atg a Met I ctg	aa t ys S agg	ca t Ser I	tc a Phe s aag	gc Ser 15 gcc	ic	114
ccag cttg cgg Arg	atct gaca atc Ile	gt tocations of the second sec	ttc Phe	ctc Leu -10 cct	gtc Val ctg	ttc Phe cct	ctc Leu ttg	ctc Leu ggc	gcc Ala -5 tgt	ggc ggc ggc	atg a Met I ctg Leu ttt	aad t ys S agg Arg	ca ter I	tc aphe s aag Lys 1	gc Ser 15 gcc Ala	ic	114
ccag cttg cgg Arg	atct gaca atc Ile	gt tocations of the second sec	ttc Phe	ctc Leu -10 cct	gtc Val ctg	ttc Phe cct	ctc Leu ttg	ctc Leu ggc	gcc Ala -5 tgt	ggc ggc ggc	atg a Met I ctg Leu ttt	aad t ys S agg Arg	ca ter I	tc aphe s aag Lys 1	gc Ser 15 gcc Ala		114
ccag cttg cgg ; Arg ; gct ; Ala ;	atctgaca atc Ile ccc Pro	ctc Leu tca Ser 5	ttc Phe gcc Ala	ctc Leu -10 cct Pro	gtc Val ctg Leu	ttc Phe cct Pro	ctc Leu ttg Leu 10 ctg	ctc Leu ggc Gly	gcc Ala -5 tgt Cys	ggc ggc ggc Gly	atg a Met I ctg Leu ttt Phe	agg Arg ccg Pro 15	tcc Ser I tcc Ser gac Asp	aag Lys 1 atg Met	er 15 gcc Ala gcc Ala		114
cgg Gct Arg Cac His	atct gaca atc Ile ccc Pro ccc Pro 20	ctc Leu tca Ser 5 tct	ttc Phe gcc Ala gag Glu	ctc Leu -10 cct Pro act Thr	gtc Val ctg Leu tcc Ser	ttc Phe cct Pro cct Pro 25	ctc Leu ttg Leu 10 ctg Leu	ctc Leu ggc Gly aag	gcc Ala -5 tgt Cys ggt Gly	ggc Gly ggc Gly gct Ala	atg a Met I ctg Leu ttt Phe tct Ser 30	agg Arg ccg Pro 15 gaa Glu	tcc Ser I tcc Ser gac Asp aat	aag Lys 1 atg Met tcc Ser	gc Ser 15 gcc Ala gcc Ala aaa Lys		114 162 210
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cgg ctgg gct Arg Cac His cga Arg Arg	atct gaca atc Ile ccc Pro ccc Pro gat	ctc Leu tca Ser 5 tct Ser	ttc Phe gcc Ala gag Glu	ctc Leu -10 cct Pro act Thr	gtc Val ctg Leu tcc Ser	ttc Phe cct Pro cct Pro 25 gaa	ctc Leu ttg Leu 10 ctg Leu	ctc Leu ggc Gly aag Lys	gcc Ala -5 tgt Cys ggt Gly	ggc Gly ggc Gly gct Ala act Thr	atg a Met I ctg Leu ttt Phe tct Ser 30 cct	agg Arg ccg Pro 15 gaa Glu	tcc Ser I tcc Ser gac Asp aat Asn	aag Lys 1 atg Met tcc Ser	gc Ser 15 gcc Ala gcc Ala aaa Lys		114 162 210 258
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cgg ctgg gct Arg cac His cga Arg Arg 35	atct gaca atc Ile ccc Pro ccc Pro gat Asp	ctc Leu tca Ser 5 tct Ser cgc Arg	ttc Phe gcc Ala gag Glu ctt Leu	ctc Leu -10 cct Pro act Thr aac Asn	gtc Val ctg Leu tcc Ser cca Pro 40	ttc Phe cct Pro cct Pro 25 gaa Glu	ctc Leu ttg Leu 10 ctg Leu ttt Phe	ctc Leu ggc Gly aag Lys cct Pro	gcc Ala -5 tgt Cys ggt Gly ggg Gly	ggc Gly ggc Gly gct Ala act Thr	atg a Met I ctg Leu ttt Phe tct Ser 30 cct	agg Arg ccg Pro 15 gaa Glu	tcc Ser I tcc Ser gac Asp aat Asn	aag Lys 1 atg Met tcc Ser	gc Ser 15 gcc Ala gcc Ala aaa Lys		114 162 210 258 306
cgg ctgg gct Arg cac his cga Arg 35 tcc	atct gaca atc Ile ccc Pro ccc Pro gat Asp	ctc Leu tca Ser 5 tct Ser cgc Arg	ttc Phe gcc Ala gag Glu ctt Leu	ctc Leu -10 cct Pro act Thr aac	gtc Val ctg Leu tcc Ser cca Pro 40	ttc Phe cct Pro cct Pro 25 gaa Glu	ctc Leu ttg Leu 10 ctg Leu ttt Phe	ctc Leu ggc Gly aag Lys cct Pro	gcc Ala -5 tgt Cys ggt Gly ggg	ggc Gly ggc Gly gct Ala act Thr	atg a Met I ctg Leu ttt Phe tct Ser 30 cct	agg Arg ccg Pro 15 gaa Glu	tcc Ser I tcc Ser gac Asp aat Asn	aag Lys 1 atg Met tcc Ser	gc Ser 15 gcc Ala gcc Ala aaa Lys		114 162 210 258 306
cgg ctrg gct cac cac chis cac cac cac cac cac cac cac cac cac ca	atct gaca atc Ile ccc cro ccc gat Asp Lys	ctc Leu tca Ser 5 tct Ser cgc Arg	ttc Phe gcc Ala gag Glu ctt Leu	ctc Leu -10 cct Pro act Thr aac Asn	gtc Val ctg Leu tcc Ser cca Pro 40	ttc Phe cct Pro cct Pro 25 gaa Glu	ctc Leu ttg Leu 10 ctg Leu ttt Phe	ctc Leu ggc Gly aag Lys cct Pro	gcc Ala -5 tgt Cys ggt Gly ggg Gly	ggc Gly ggc Gly gct Ala act Thr	atg a Met I ctg Leu ttt Phe tct Ser 30 cct	agg Arg ccg Pro 15 gaa Glu	tcc Ser I tcc Ser gac Asp aat Asn	aag Lys 1 atg Met tcc Ser	gc Ser 15 gcc Ala gcc Ala aaa Lys	ac	114 162 210 258 306
cgg ctgg gct Arg cac his cga Arg 35 tcc	atct gaca atc atc gaca atc alle ccc cro ccc gat Asp aag Lys > 87	ctc Leu tca Ser tct Ser cgc Arg	ttc Phe gcc Ala gag Glu ctt Leu	ctc Leu -10 cct Pro act Thr aac Asn	gtc Val ctg Leu tcc Ser cca Pro 40	ttc Phe cct Pro cct Pro 25 gaa Glu	ctc Leu ttg Leu 10 ctg Leu ttt Phe	ctc Leu ggc Gly aag Lys cct Pro	gcc Ala -5 tgt Cys ggt Gly ggg Gly	ggc Gly ggc Gly gct Ala act Thr	atg a Met I ctg Leu ttt Phe tct Ser 30 cct	agg Arg ccg Pro 15 gaa Glu	tcc Ser I tcc Ser gac Asp aat Asn	aag Lys 1 atg Met tcc Ser	gc Ser 15 gcc Ala gcc Ala aaa Lys	ac	114 162 210 258 306
cgg Arg Star Ala Cac A	atct gaca atc atle coro coro coro gat atys 87 > 26	ctc Leu tca ser tct cgc Arg cta Leu	ttc Phe gcc Ala gag Glu ctt Leu cct	ctc Leu -10 cct Pro act Thr aac Asn cat His	gtc Val ctg Leu tcc Ser cca Pro 40	ttc Phe cct Pro cct Pro 25 gaa Glu	ctc Leu ttg Leu 10 ctg Leu ttt Phe	ctc Leu ggc Gly aag Lys cct Pro	gcc Ala -5 tgt Cys ggt Gly ggg Gly	ggc Gly ggc Gly gct Ala act Thr	atg a Met I ctg Leu ttt Phe tct Ser 30 cct	agg Arg ccg Pro 15 gaa Glu	tcc Ser I tcc Ser gac Asp aat Asn	aag Lys 1 atg Met tcc Ser	gc Ser 15 gcc Ala gcc Ala aaa Lys	ac	114 162 210 258 306
cgg ct car	atct gaca atc atle coro coro coro gat atys 87 > 26	ctc Leu tca ser tct cgc Arg cta Leu	ttc Phe gcc Ala gag Glu ctt Leu cct	ctc Leu -10 cct Pro act Thr aac Asn cat His	gtc Val ctg Leu tcc Ser cca Pro 40	ttc Phe cct Pro cct Pro 25 gaa Glu	ctc Leu ttg Leu 10 ctg Leu ttt Phe	ctc Leu ggc Gly aag Lys cct Pro	gcc Ala -5 tgt Cys ggt Gly ggg Gly	ggc Gly ggc Gly gct Ala act Thr	atg a Met I ctg Leu ttt Phe tct Ser 30 cct	agg Arg ccg Pro 15 gaa Glu	tcc Ser I tcc Ser gac Asp aat Asn	aag Lys 1 atg Met tcc Ser	gc Ser 15 gcc Ala gcc Ala aaa Lys	ac	114 162 210 258 306
cgg Arg Star Ala Cac A	atct gatc atc atc atc coro coro coro coro atc coro coro atc coro coro atc coro coro atc coro	ctc Leu tca ser tct cgc Arg cta Leu	ttc Phe gcc Ala gag Glu ctt Leu cct	ctc Leu -10 cct Pro act Thr aac Asn cat His	gtc Val ctg Leu tcc Ser cca Pro 40	ttc Phe cct Pro cct Pro 25 gaa Glu	ctc Leu ttg Leu 10 ctg Leu ttt Phe	ctc Leu ggc Gly aag Lys cct Pro	gcc Ala -5 tgt Cys ggt Gly ggg Gly	ggc Gly ggc Gly gct Ala act Thr	atg a Met I ctg Leu ttt Phe tct Ser 30 cct	agg Arg ccg Pro 15 gaa Glu	tcc Ser I tcc Ser gac Asp aat Asn	aag Lys 1 atg Met tcc Ser	gc Ser 15 gcc Ala gcc Ala aaa Lys	ac	114 162 210 258 306
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cttgatgctt ttgagaaatg aataatgttt tctccctttt aaatggtagt acagc atg
                                                                       238
cac act ttt ctg tgc ttg ctt ttt tat ctc ata gta tct tgt gga gct
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His Thr Phe Leu Cys Leu Leu Phe Tyr Leu Ile Val Ser Cys Gly Ala
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gtt ttc tta aca gtc cct tct ccc caa gg
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Val Phe Leu Thr Val Pro Ser Pro Gln
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csb new cet eet eea etg mae agg gwe tey ete eea gee tgt get gae
                                                                       101
Xaa Xaa Pro Pro Pro Leu Xaa Arg Xaa Ser Leu Pro Ala Cys Ala Asp
                 -25
                                     -20
tca atc atc ctc tgm ctc tgm ttc cct ggg atc ctc ggw caa gct cac
                                                                       149
Ser Ile Ile Leu Xaa Leu Xaa Phe Pro Gly Ile Leu Gly Gln Ala His
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ctg mac tct gag cag tgg aca cag tac cta
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Leu Xaa Ser Glu Gln Trp Thr Gln Tyr Leu
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-5	·	1	110 Deu	5	FIO Ded	
ser Pro Leu Leu 10		_		<i>*</i>	·	423
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cca ggg aga ggg Pro Gly Arg Gly	cag aca cag Gln Thr Gln 1	cag gag Gln Glu 5	gaa gag Glu Glu	gaa gag gac Glu Glu Asp 10	gag gac Glu Asp	157
cac ggg cca gat His Gly Pro Asp 15	gac tac gac Asp Tyr Asp	gag gaa Glu Glu 20	gat gag Asp Glu	gat gag gtt	gaa gag Glu Glu	205
gag gag acc aac Glu Glu Thr Asn 30	agg ctc cct Arg Leu Pro 35	ggt ggc Gly Gly	agg agc Arg Ser	aga gtg ctg Arg Val Leu 40	ctg cgg Leu Arg	253
tgc tac acc tnk Cys Tyr Thr Xaa 45	Xaa Ser Leu 50	ccc agg Pro Arg	gac gag Asp Glu 55	cgc tgc aac Arg Cys Asn	ctg acg Leu Thr 60	301
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	tottottaca cagtgrotga gaacatttac attatagata agtagtacat ggtggataac ttotactttt aggaggacta ototottotg acagtoctag actggtotto tacactaaga	180
	cace atg aag gag tat gtg etc eta tta tte etg get ttg tge tet gee	240
	Met Lys Glu Tyr Val Leu Leu Phe Leu Ala Leu Cys Ser Ala	289
	-15 -10 -5	
	aaa ccc ttc ttt agc cct tca cac atc gca ctg aag aat atg atg ctg	337
	Lys Pro Phe Phe Ser Pro Ser His Ile Ala Leu Lys Asn Met Met Leu	
	1 5 10 15	
	aag gat atg gaa gac aca gat gat gat gat gat gat gat gat	385
	Lys Asp Met Glu Asp Thr Asp Asp Asp Asp Asp Asp Asp Asp Asp 25	
	gat gat gag gac aac tet ett tet eea aca aga gag eea aga age	433
	Asp Asp Asp Glu Asp Asn Ser Leu Phe Pro Thr Arg Glu Pro Arg Ser	433
	35 40 45	
	cat ttt ttt cca ttt gat ctg ttt cca atg tgt cca ttt gga tgt cag	481
	His Phe Phe Pro Phe Asp Leu Phe Pro Met Cys Pro Phe Gly Cys Gln	
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	Phe Leu Leu Leu Val Ala Ala Pro Arg Trp Ala Met Ser Gln Val Gln	
	-10 -5 1	
	ctg cag gaa tcg ggc ccg aga ctg gtg aaa cct tcg ggg acc ctg tcc	149
	Leu Gln Glu Ser Gly Pro Arg Leu Val Lys Pro Ser Gly Thr Leu Ser	
	5 10 15	
	ctc acc tgc agt gtc tct ggt ggc tcc atg gcc act agt gac tgg tgg Leu Thr Cys Ser Val Ser Gly Gly Ser Met Ala Thr Ser Asp Trp Trp	197
	20 25 30 35	
	agt tgg ttt cga cag acm ccg gag aag ggt ctg gag tgg att ggg gaa	245
	Ser Trp Phe Arg Gln Thr Pro Glu Lys Gly Leu Glu Trp Ile Gly Glu	

40 45 atc ttt cag act ggg ccc acc aat tac aac ccg tcc ctc aag agc cgc Ile Phe Gln Thr Gly Pro Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg 55 60 gtc tcc atg tca gtg gac atg tcc aag a 321 Val Ser Met Ser Val Asp Met Ser Lys <210> 95 <211> 402 <212> DNA <213> Homo sapiens <220> 1 <221> CDS <222> 15..401 <221> sig\_peptide <222> 15..92 <223> Von Heijne matrix score 9.5 seq FLLLVAAPRWALS/QL <400> 95 getttetgag agte atg gat etc acg tgc aag aaa atg aag cae etg tgg 50 Met Asp Leu Thr Cys Lys Lys Met Lys His Leu Trp -25 -20 tto tto cto ctg ctg gtg gcg gct ccc aga tgg gcc ctg tcc caa ctg 98 Phe Phe Leu Leu Val Ala Ala Pro Arg Trp Ala Leu Ser Gln Leu -10 - 5 cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tcg gag acc ctg 146 Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu 10 tcc ctc acg tgc act gtc tct ggt gaa tcc atc acc act aat tca ttc 194 Ser Leu Thr Cys Thr Val Ser Gly Glu Ser Ile Thr Thr Asn Ser Phe 25 30 tgc tgg gcc tgg atc cgc cag ccc ccg ggg aag ggg ctg gaa tgg ctt 242 Cys Trp Ala Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu 40 ggg act gta tgt tat ggt ggg acc acc tac krc aac keg tee etg aag 290 Gly Thr Val Cys Tyr Gly Gly Thr Thr Tyr Xaa Asn Xaa Ser Leu Lys 60 agt cga gtc aag tta tcg ttg gac acg tcc acg aat cag ttc tcc ctg 338 Ser Arg Val Lys Leu Ser Leu Asp Thr Ser Thr Asn Gln Phe Ser Leu 70 75 aag gtc acc tet atg acc gec gga gac geg get gtc cat tac tgt geg 386 Lys Val Thr Ser Met Thr Ala Gly Asp Ala Ala Val His Tyr Cys Ala 90 ggg ctg cgt gtt agt g 402 Gly Leu Arg Val Ser 100 <210> 96 <211> 315 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 118..315

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												_		_	tac	165
			-60	)				-55		٠,	_		-50	ı	Tyr	•
															aaa	213
		-45	5				-40	,		_		-35	_		Lys	
gcc	cac	aaa	cat	: tcc	ato	gtg	ato	gca	ttc	tgg	gtg	agc	ctg	gct	gcc	261
	-30					-25					-20				Ala	
															gcs	309
	Val	Val	. Leu	Leu	Pne 10-		lle	Leu	Leu		Met	Ser	Trp	Ser	Ala	
-15	ccg				- 10					5					1	315
	Pro															313
	0 > 9						٠			•						;
	1 > 4 2 > D															
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		- 1			-											
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															catcac	60
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•••		- F			15	- 5		·		10				- !		
gtc	cag	tcm	cag	gks	cas	ctg	gwg	cag	tcţ	999	gct	gag	gtg	aag	aag	157
Val	Gln	Ser	Gln	Xaa	Xaa	Leu		Gln	Ser	Gly	Ala		Val	Lys	Lys	
cct	~~~	tee	tca	ata	222	ata	5	+~~	220	001	tat	10	~~~	250		205
														Ile		205
	15	-			~, 5	20	501	0,0			25	U1,	Cly	110	2144	
agc	asc	tat	agc	ttc	aac	tgg	gtg	cgm	cag	gcc	cct	gga	cag	999	ttt	253
	Xaa	Tyr	Ser	Phe	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Phe	
30	,				35					40					45	
														tac Tyr		301
GIU	TTP	Deu	GIY	50	116	116	PIU	TIG	ьеи 55	GIA	тте	1111	ASI	1yr 60	wig	*
gag	aaq	ttt	cgg		aga	ctc	acq	atc		qtq	gac	aaa	tcc	acg	cat	349
														Thr		
att	att	tac		gao	cao.	age	agt		aca	tat	aca	gac	-	gcc	ata	397
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		80		·			85					90			: <del>-</del>	
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Tyr	_	Cys	Ala	Lys	Pro		Met	Thr	Ser	Glu		Arg	Val	Tyr	Tyr	
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	Tyr Phe Val Phe Tyr Leu	ctg 172 Leu
20 ctt ttg tca gcg ttt acg agt caa aca	-15	
Leu Leu Ser Ala Phe Thr Ser Gln Thr	Val Ser Gly Gln Arg Lys L 1	ys
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*	÷1.	5
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-10 -	5 1	
eag ctc cag gag tcc ggc tca gga ctg g Sin Leu Gin Glu Ser Gly Ser Gly Leu G 5 10	lag aag oot toa cag acc o lu Lys Pro Ser Gln Thr Le 15	tg 150 eu
cc ctc acc tgc tct gtc tct ggt ggc t	cc atc agt agt gat gat ti	ig 198
Ser Leu Thr Cys Ser Val Ser Gly Gly S 20 25	er Ile Ser Ser Asp Asp Le	∍u
cg tgg agc tgg atc cga cag ccg cca g	gg aag ggc ctg gag tgg at	t 246
Ser Trp Ser Trp Ile Arg Gln pro Pro G 5 40		
IGC tac att tat caa aat gag agg acc c	5,	

•

Xaa Ser Ser Lys Ser

Gly Tyr Ile Tyr Gln Asn Glu Arg Thr Leu Tyr Asn Pro Ser Leu Lys 55 60 agt cga gcc gcc att tca gtg gac agg tcc aag aac cag ttc tcc ctg Ser Arg Ala Ala Ile Ser Val Asp Arg Ser Lys Asn Gln Phe Ser Leu 75 aaa ctg acc tct gtg acc gcc gcg gac atg gcc gta tat tac tgt gcc 390 Lys Leu Thr Ser Val Thr Ala Ala Asp Met Ala Val Tyr Tyr Cys Ala 90 95 acc agt gtc atg awt too tit ggg ggc gtt ctc gtc cct aat ctg tit 438 Thr Ser Val Met Xaa Ser Phe Gly Gly Val Leu Val Pro Asn Leu Phe 105 ttg act act ggg gcc agg gaa tct cgt ca 467 Leu Thr Thr Gly Ala Arg Glu Ser Arg 120 <210> 100 <211> 504 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 39..503 <221> sig\_peptide <222> 39..95 <223> Von Heijne matrix score 9.30000019073486 seq FLLLVAGPRWVLS/QV <400> 100 aatactttct gagagtcctg gacctcctgt gcaagaac atg aaa cac ctg tgg ttc 56 Met Lys His Leu Trp Phe ttc ctc ctg ctg gtg gca ggt ccc aga tgg gtc ctg tcc cag gtg cag 104 Phe Leu Leu Val Ala Gly Pro Arg Trp Val Leu Ser Gln Val Gln ctg sdk gag tcg ggc cca aga ctg gtg aag cct tca cag acc ctg tcc 152 Leu Xaa Glu Ser Gly Pro Arg Leu Val Lys Pro Ser Gln Thr Leu Ser 10 ctc acc tgc act gta tct ggg gcc tcc gtc agc agt cgt ggg tac tat 200 Leu Thr Cys Thr Val Ser Gly Ala Ser Val Ser Ser Arg Gly Tyr Tyr 25 30 tgg acc tgg atc cgc cag ctc cca ggg aag ggc ctg gag tgg att ggc 248 Trp Thr Trp Ile Arg Gln Leu Pro Gly Lys Gly Leu Glu Trp Ile Gly 45 tac atc tgk tac act ggg agc acc ttc tac aac ccg tcc ctc aag agt 296 Tyr Ile Xaa Tyr Thr Gly Ser Thr Phe Tyr Asn Pro Ser Leu Lys Ser 60 cga tta acc ata tca ata gac acg tct aag aat cag ttc tcc ctg aac 344 Arg Leu Thr Ile Ser Ile Asp Thr Ser Lys Asn Gln Phe Ser Leu Asn ctg agg tct gtg act acc gcg gac acg gcc gtc tat tac tgt gcg aga 392 Leu Arg Ser Val Thr Thr Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg 90 gac cat ttc gat ctt cta ttc gac ccc tgg ggc cag gga acc ctg gtc 440 Asp His Phe Asp Leu Leu Phe Asp Pro Trp Gly Gln Gly Thr Leu Val 105 110 ace gto tee tet gem tee ace aag gge eea teg gto tto eec etg gea 488 Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala 125 scc tcc tcc aag agc a 504

135

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tgttcgatgc cacgctgacc cagggta atg gcc tgc cga gag agg ccg cgg ccc
                                                                       174
                               Met Ala Cys Arg Glu Arg Pro Arg Pro
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ctt ctg tgg agg tct agg gga agg ttt ttt aat tgg gga aag ctg ttt
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Leu Leu Trp Arg Ser Arg Gly Arg Phe Phe Asn Trp Gly Lys Leu Phe
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                             -25
                                                 -20
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Phe Cys Phe Val Leu Xaa Leu Phe Cys Phe Val Phe Glu Ala Glu Ser
    -15
                         -10
ege tet gte gee eag get gga gtg eag tgg ege tat tte gge tea eta
                                                                       318
Arg Ser Val Ala Gln Ala Gly Val Gln Trp Arg Tyr Phe Gly Ser Leu
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caa gct ttg cct ccc tgg
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Gln Ala Leu Pro Pro Trp
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ttggcacctt tgttgaaaaa cagttggcca tag atg cat gaa ttt att tct ggg
                                                                      234
                                     Met His Glu Phe Ile Ser Gly
                                          -20
ttc ttt att ctc ttt cat tgg tct ctg tgt ttg tgt tta tgc caa tac
                                                                      282
Phe Phe Ile Leu Phe His Trp Ser Leu Cys Leu Cys Leu Cys Gln Tyr
cat gcc g
                                                                      289
His Ala
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                                                                         60
 tattctacct ctcccttgct ctttccagac caggcttggg acataacact aacacccttt
                                                                        120
 teettteatt teatetettg teetteagte atteetaaac attgacaybe attgagttee
 ttggctctgg ccatagtcct ttctcccttt cccctctggg gcatcaaata gtgattacag
 tatecacagg g atg gea tat gee att tea eea ttt cae agt tee tgg aat
                                                                        290
              Met Ala Tyr Ala Ile Ser Pro Phe His Ser Ser Trp Asn
                       -40
                                           -35
 cca ctt ttc act tct cat aaa gct tca gca agc cat tct cat ctt ggg
                                                                        338
 Pro Leu Phe Thr Ser His Lys Ala Ser Ala Ser His Ser His Leu Gly
                  -25
                                      -20
 ttg ctt gtt tgc cta ttt gct gtt aca tcc att ctc tgc tcc tca
                                                                        383
 Leu Leu Val Cys Leu Phe Ala Val Thr Ser Ile Leu Cys Ser Ser
             -10
 <210> 104
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<221> sig_peptide
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       seg PVLLLALLGFILP/LP
 <221> misc_feature
 <222> 83
 <223> n=a, g, c or t
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 agaaagagat taccagccac agacgggtc atg agc ccg gta tta ctg ctg gcc
                                                                        53
                                 Met Ser Pro Val Leu Leu Leu Ala
                                  -15
                                                      -10
 ctc ctg ggg ttc atc ctc cca ctg cca ggn agt gca rgc gct gss tck
                                                                       101
 Leu Leu Gly Phe Ile Leu Pro Leu Pro Gly Ser Ala Xaa Ala Xaa Ser
         - 5
 gcc agt ttg 99a cag ttc agc atg tgt gga agg tgt ccg acm tgc ccc
                                                                       149
 Ala Ser Leu Gly Gln Phe Ser Met Cys Gly Arg Cys Pro Thr Cys Pro
                                         20
                     15
 ggc aat gga ccc cta aga aca cca gct gcg aca sgg vtt rgg gtg cca
                                                                       197
 Gly Asn Gly Pro Leu Arg Thr Pro Ala Ala Thr Xaa Xaa Xaa Val Pro
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35
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 gga cac gtt gat gc
                                                                       211
 Gly His Val Asp
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                                                                        52
                              Met Ala Thr Ala Met Asp Trp Leu
                                            -20
 ccg tgg tct tta ctg ctt ttc tcc ctg atg tgt gaa aca agc gcc ttc
                                                                       100
 Pro Trp Ser Leu Leu Leu Phe Ser Leu Met Cys Glu Thr Ser Ala Phe
                     -10
                                         -5
 tat gtg cct ggg gtc gcg cct atc aac ttc cac cag aac gat ccc gta
                                                                       148
Tyr Val Pro Gly Val Ala Pro Ile Asn Phe His Gln Asn Asp Pro Val
                                 10
 gaa atc aag gct gtg aag ctc acc agc tct cga acc cag cta cct tat
                                                                       196
Glu Ile Lys Ala Val Lys Leu Thr Ser Ser Arg Thr Gln Leu Pro Tyr
        20
                            25
gaa tac tat tca ctg ccc ttc tgc cag ccc agc aag ata acc tac aag
                                                                       244
Glu Tyr Tyr Ser Leu Pro Phe Cys Gln Pro Ser Lys Ile Thr Tyr Lys
                         40
                                             45
gca gag aat ctg gga gag gtg ctg aga ggg gac cgg att gtc aac acc
                                                                       292
Ala Glu Asn Leu Gly Glu Val Leu Arg Gly Asp Arg Ile Val Asn Thr
                    55
                                         60
cct ttc cag gtt ctc atg aac agc gag aag aag tgt gaa gtt ctg tgc
                                                                       340
Pro Phe Gln Val Leu Met Asn Ser Glu Lys Lys Cys Glu Val Leu Cys
                                     75
age cag tee aac aag eea gtg ace etg aca gtg gag eag age ega etc
                                                                       388
Ser Gln Ser Asn Lys Pro Val Thr Leu Thr Val Glu Gln Ser Arg Leu
                                 90
gtg gcc gag cgg atc aca gaa gac tac tac gtc cac ctc att gct gac
                                                                       436
Val Ala Glu Arg Ile Thr Glu Asp Tyr Tyr Val His Leu Ile Ala Asp
                            105
                                                 110
aac etg eet gtg gee ace gge tgg age tet act eea ace gag aca geg
                                                                       484
Asn Leu Pro Val Ala Thr Gly Trp Ser Ser Thr Pro Thr Glu Thr Ala
    115
                         120
                                             125
atg aca ag
                                                                       492
Met Thr
130
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                                                                        55
                                             Met Pro Ser Pro Cys
ctg atc tct ctt caa tgt gct cat gtg tcc ctt ggc tta cag tat
                                                                       103
Leu Ile Ser Leu Leu Gln Cys Ala His Val Ser Leu Gly Leu Gln Tyr
             -10
                                 -5
cca tgc stt ctc ctt ctc cct cc
                                                                       126
Pro Cys Xaa Leu Leu Leu Pro
    5
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<221> sig_peptide
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      seq LVLAAFCLGIASA/VP
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accagaccgc ggacgtctgt aatctcagag gcttgtttgc tgagggtgcc tgcgcastgc
                                                                       60
gacggctgct ggttttgaaa c atg aat ctt tcg ctc gtc ctg gct gcc ttt
                                                                      111
                        Met Asn Leu Ser Leu Val Leu Ala Ala Phe
                                -15
tgc ttg gga ata gcc tcc gct gtt cca aaa ttt gac caa aat ttg gat
                                                                      159
Cys Leu Gly Ile Ala Ser Ala Val Pro Lys Phe Asp Gln Asn Leu Asp
aca aag tgg tac cag tgg aag gca aca cac aga aga tta tat ggc gcg
                                                                      207
Thr Lys Trp Tyr Gln Trp Lys Ala Thr His Arg Arg Leu Tyr Gly Ala
                    15
                                        20
aat gaa gaa gga tgg agg aga gca gcg tgg gag gg
                                                                      242
Asn Glu Glu Gly Trp Arg Arg Ala Ala Trp Glu
                30
<210> 108
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     score 9
     seq WVFLVAIFTGVHC/EV
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agctctggga gaggagccc agccgtgaga ttcccagaag tttccacttg gtgatcag ctgaacacag accaccaacc atg gag ttt ggc ctt aat tgg gtt ttc ctt g Met Glu Phe Gly Leu Asn Trp Val Phe Leu V	tt 113
gct att ttt aca ggt gtc cac tgt gag gtg cag ttg gtg gag tct ggg Ala Ile Phe Thr Gly Val His Cys Glu Val Gln Leu Val Glu Ser Gly -5	,
gga gac ctg gta cag cca ggg cgg tcc ctg aga ctc tcc tgt aca gct Gly Asp Leu Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Thr Ala 10 15 20	,
tct gga ttc acc ttt ggt gat tat gcc atg acc tgg ttc cgc cag gct Ser Gly Phe Thr Phe Gly Asp Tyr Ala Met Thr Trp Phe Arg Gln Ala 25 30 35 40	ı
tca ggg aag cga ctg gag tgg cta ggt ttc att aga aat aga ggt tcs Ser Gly Lys Arg Leu Glu Trp Leu Gly Phe Ile Arg Asn Arg Gly Ser 45 50 55	305
ggt ggg tca gca gag tac ggc gcg tct gtg a Gly Gly Ser Ala Glu Tyr Gly Ala Ser Val 60 65	336
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-15 -10 -5 ata cac ata aac cgt atg aat gta agg aat gtg gga aat act tta gtc Ile His Ile Asn Arg Met Asn Val Arg Asn Val Gly Asn Thr Leu Val 1 5 10	
gta gtg caa atc tta ttc agc atc aga gta ttc ata ctg gag aga aac Val Val Gln Ile Leu Phe Ser Ile Arg Val Phe Ile Leu Glu Arg Asn	146
15 20 25 30	
15 20 25 30 cct ttg aat gtg gg Pro Leu Asn Val	160
cct ttg aat gtg gg	160
cct ttg aat gtg gg Pro Leu Asn Val  <210> 110 <211> 527 <212> DNA	160

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<222> 59..115'
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atg gac tgg acc tgg aga atc ctc ctc ttg gtg gca gca gcc aca gat
                                                                      106
Met Asp Trp Thr Trp Arg Ile Leu Leu Leu Val Ala Ala Ala Thr Asp
                -15
                                  -10
gcc tcc tcc cag atg cag ctg ttg cag tct ggg cct gaa gtg aag aag
                                                                      154
Ala Ser Ser Gln Met Gln Leu Leu Gln Ser Gly Pro Glu Val Lys Lys
                            5
act ggg tcc tca gtg aaa ctt tcc tgc acg gcc tcc ggc gac acc ctc
                                                                      202
Thr Gly Ser Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Asp Thr Leu
                        20
gcc tac cac tac ctg cac tgg gtg cga cag gcc ccc gga caa gcg ctt
                                                                      250
Ala Tyr His Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Ala Leu
                    35
gag tgg atg gga tgg atc aca cct ttc agt gga gac acc aac ttc gca
                                                                      298
Glu Trp Met Gly Trp Ile Thr Pro Phe Ser Gly Asp Thr Asn Phe Ala
                50
                                    55
cag cga ttc cag gac aga ctc acc ttc acc agg gac agg tct atg agc
                                                                      346
Gln Arg Phe Gln Asp Arg Leu Thr Phe Thr Arg Asp Arg Ser Met Ser
          , 65
                                70
aca gtc tac atg acc ctg acc agc ctg ata tct gaa gac aca gcc atg
                                                                      394
Thr Val Tyr Met Thr Leu Thr Ser Leu Ile Ser Glu Asp Thr Ala Met
                            85
                                                90
tat tac tgt gcc act gat gga cgt cgc acc aac cgt ctt ttt gaa ca
Tyr Tyr Cys Ala Thr Asp Gly Arg Arg Thr Asn Arg Leu Phe Glu
    95
                        100
<210> 113
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   seq LGCLLWLLTHIKA/QD
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<222> 290..292 <223> n=a, g, c or t

cagtttcagt ttctctcct tcctagtaga gacaaaaagg agacacattt tatccgtgca tccaaagact ccgatgttgg tcatggactt gggaagacag tcttcccttg gcgtttgatc actgcggaga tgccttcctt gatcattcac ccacattccc ttg atg gca ggt caa  Met Ala Gly Gln .	60 120 175
ttg ctg gga tgc ctg ctt tgg ctg ctc acc cac att aaa gcc cag gac Leu Leu Gly Cys Leu Leu Trp Leu Leu Thr His Ile Lys Ala Gln Asp -10 -5 1	223
tca gtc agg gat gcc tac tgg aag act ggt agc tgc cca cct cca ttt Ser Val Arg Asp Ala Tyr Trp Lys Thr Gly Ser Cys Pro Pro Pro Phe 5 10 15	271
ctc cat gtg tct acc ttc nnn kkt aaa ctt acc ttc tcc act aag ggc Leu His Val Ser Thr Phe Xaa Xaa Lys Leu Thr Phe Ser Thr Lys Gly 20 25 30	319
aac ctt ctg cat tcc att cct ctc tct tcc ccc tta gcc tgt gtt ctt Asn Leu Leu His Ser Ile Pro Leu Ser Ser Pro Leu Ala Cys Val Leu 35 40 45 50 ag	367
	369
<210> 114 <211> 334	٠.
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<220> <221> CDS <222> 20334	. •
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seq LFLMLLGELGVFA/SY <221> misc feature	
<222> 295 <223> n=a, g, c or t	
	٠,
<pre>&lt;400&gt; 114 agctctgaat tgggaaggg atg aag gag gct gtg cct ccg ggt tgc acg aag</pre>	<b>52</b> .
agt ccg agt cat ttc tca gaa ggt ttt gat agg tgg gcc tta gag gag Ser Pro Ser His Phe Ser Glu Gly Phe Asp Arg Trp Ala Leu Glu Glu -80 -75 -70 -65	100
	148
acg ccg ccg gaa aac ctg att ggc gcc ctc ttg gcg atc ttc ggg cac Thr Pro Pro Glu Asn Leu Ile Gly Ala Leu Leu Ala Ile Phe Gly His -60 -55 -50	
Thr Pro Pro Glu Asn Leu Ile Gly Ala Leu Leu Ala Ile Phe Gly His -60 -55 -50 ctc gtg gtc agc att gca ctt aac ctc cag aag tac tgc cac atc cgc Leu Val Val Ser Ile Ala Leu Asn Leu Gln Lys Tyr Cys His Ile Arg	196
Thr Pro Pro Glu Asn Leu Ile Gly Ala Leu Leu Ala Ile Phe Gly His -60 -55 -50  ctc gtg gtc agc att gca ctt aac ctc cag aag tac tgc cac atc cgc Leu Val Val Ser Ile Ala Leu Asn Leu Gln Lys Tyr Cys His Ile Arg	196 244
Thr Pro Pro Glu Asn Leu Ile Gly Ala Leu Leu Ala Ile Phe Gly His -60 -55 -50  ctc gtg gtc agc att gca ctt aac ctc cag aag tac tgc cac atc cgc  Leu Val Val Ser Ile Ala Leu Asn Leu Gln Lys Tyr Cys His Ile Arg -45 -40  ctg gca ggc tcc aag gat ccc cgg gcc tat ttc aag acc aag aca tgg  Leu Ala Gly Ser Lys Asp Pro Arg Ala Tyr Phe Lys Thr Lys Thr Trp	

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 <221> CDS
 <222> 21..152
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                       Met Ala Phe Leu Trp Leu Leu Ser Cys Trp Ala
                                   -15
 ctc ctg ggt acc acc ttc ggc tgc ggg gtc ccc gcc atc cac cct ggc
                                                                       101
 Leu Leu Gly Thr Thr Phe Gly Cys Gly Val Pro Ala Ile His Pro Gly
         ~5
 tgc caa ctg agc ccg cgg ctc cct ccg acc ctg ctc ccc aca gag cgc
 Cys Gln Leu Ser Pro Arg Leu Pro Pro Thr Leu Leu Pro Thr Glu Arg
 10
                     15
                                         20
999 g
                                                                       153
Gly
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                                                                        55
                                                    Met Ala Pro
ttt caa aac ttc ctt tgg ctt ttc ttt gtg ctt aat tta ggw agt ttt
                                                                       103
Phe Gln Asn Phe Leu Trp Leu Phe Phe Val Leu Asn Leu Gly Ser Phe
        -15
                             -10
get ttt age tea mit eed aat tet ett tit tae aca att eat tit ggt
                                                                       151
Ala Phe Ser Ser Xaa Pro Asn Ser Leu Phe Tyr Thr Ile His Phe Gly
                                        10
cct aat ttc ttt act tta cta tat aaa caa ggt gct gaa atg tgt gtg
                                                                      .199
Pro Asn Phe Phe Thr Leu Leu Tyr Lys Gln Gly Ala Glu Met Cys Val
                20
tat gta ttt aac ttc ctc tac cca ttt gct ctt ggt tat ttc ttc agt
                                                                      247
Tyr Val Phe Asn Phe Leu Tyr Pro Phe Ala Leu Gly Tyr Phe Phe Ser
                                40
tat gat att ctg gat ttg cca gtc akt gtc cgt cct cct agc ggg
                                                                      292
Tyr Asp Ile Leu Asp Leu Pro Val Xaa Val Arg Pro Pro Ser Gly
                            55
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actgaaactt totgottgag otottgtttt gocaggotga tggggotgag gtgcaccotc
                                                                      120
tgaggaaaag ctgtaaatac atg gat ttt acc caa tgc cat tcc ctt ctt tta
                                                                       173
                       Met Asp Phe Thr Gln Cys His Ser Leu Leu Leu
                       -35
                                           -30
agg gtt gaa tat tot oca gtg tot gto tgc ttt tta tta ott too gtt
                                                                       221
Arg Val Glu Tyr Ser Pro Val Ser Val Cys Phe Leu Leu Ser Val
                 -20
                                     -15
gcc ttc aat cag ttg gtt ttt gct ttg tat cca ata caa gct acw btc
                                                                       269
Ala Phe Asn Gln Leu Val Phe Ala Leu Tyr Pro Ile Gln Ala Thr Xaa
tgt ttc tct dda gtt tct ctc cct ttc ccc gct ca
                                                                      304
Cys Phe Ser Xaa Val Ser Leu Pro Phe Pro Ala
                         15
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<221> sig_peptide
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<223> Von Heijne matrix
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      seg LLLLACGVPSLWP/FA
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                                                                       60
ggctgcctgc ccatc atg ctc ttg ctc ctg ctg gcc tgt ggt gtt ccc agc
                                                                      111
                 Met Leu Leu Leu Leu Ala Cys Gly Val Pro Ser
                 -15
ctg tgg ccc ttt gcw ctt gct ctc tta aag acc c
                                                                      145
Leu Trp Pro Phe Ala Leu Ala Leu Leu Lys Thr
            1
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60

205

386

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tgtatcccag ggataaagcc tacttgattg taatggataa gcttcatgat gtgctgctga 120 atttggtttg ccagtatttt gttaaggatt tttacatca atg ttc att gag aat 174 Met Phe Ile Glu Asn att ggv ctg aag ttt tct ttt ttg ttg ttg cat ctc tgc cag gtt ttg

222 Ile Gly Leu Lys Phe Ser Phe Leu Leu Leu His Leu Cys Gln Val Leu -15 -10 cta tca aga cga gct ggt acc att cct act gaa aca att cca aaa aaa 270

Leu Ser Arg Arg Ala Gly Thr Ile Pro Thr Glu Thr Ile Pro Lys Lys

ttg agg agg aga gac ggg 288 Leu Arg Arg Asp Gly

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<211> 386

<212> DNA

<213> Homo sapiens

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<222> 71..385

<221> sig\_peptide

<222> 71..142

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tgg ggc tcc ata ttc gac tgt cag ggg agc ctg att gcg gcc tat ttg Trp Gly Ser Ile Phe Asp Cys Gln Gly Ser Leu Ile Ala Ala Tyr Leu

10 15 ctt ctg cct ctg ggg ttt gtg atc ctt ctg agt gga att ttc tgg agc 253 Leu Leu Pro Leu Gly Phe Val Ile Leu Leu Ser Gly Ile Phe Trp Ser

aac tat cgc cag gtg act gaa agc aaa gga gtg ttg agg cac atg ctc 301 Asn Tyr Arg Gln Val Thr Glu Ser Lys Gly Val Leu Arg His Met Leu 45

cga caa cac ctt gct cat ggg gcc ctg ccc gtg gcc aca gta gac agt 349

Arg Gln His Leu Ala His Gly Ala Leu Pro Val Ala Thr Val Asp Ser 60 gct gct ctt ctg aaa atc atg tgt aag car ttg ctt t

Ala Ala Leu Leu Lys Ile Met Cys Lys Gln Leu Leu

<210> 121

<211> 190

77

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seq LTCTSSLLSFALG/RS	
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Met Lys Val Glu Glu Glu	
aag ctg tat cga ttg ttg aga tct ggc gac ttg ttt aaa ttt cat cag	102
Lys Leu Tyr Arg Leu Leu Arg Ser Gly Asp Leu Phe Lys Phe His Gln	102
-35 -30 -25	
cet cae tte tat gaa ete tea gge ete aeg tgt ace age tet etg ete	150
Pro His Phe Tyr Glu Leu Ser Gly Leu Thr Cys Thr Ser Ser Leu Leu -20 -15 -10	•
tee tit gee itg gga egt tee ate eet gga agt tie eea g	190
Ser Phe Ala Leu Gly Arg Ser Ile Pro Gly Ser Phe Pro	
-5 1 5	
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score 8.5	
seq LLLFSGAVALIQT/WA	
.400. 122	
<400> 122 agattetece cagaegeeaa ggttgegggt c atg gag tee ega acc ete ete	52
Met Glu Ser Arg Thr Leu Leu	
-15	
ctg ctg ttc tcg gga gcc gtg gcc ctg atc cag acc tgg gca ggt gag	100
Leu Leu Phe Ser Gly Ala Val Ala Leu Ile Gln Thr Trp Ala Gly Glu -10 -5 1	
tgc ggg gtc ggg agg gaa aag gcc tct gcg gga agg agc gag ggg ccc	148
Cys Gly Val Gly Arg Glu Lys Ala Ser Ala Gly Arg Ser Glu Gly Pro	
5 10 15 20	
gcc cgg agg agt aaa tct gca cat ata kbt aat tac aga tta caa tta	196
Ala Arg Arg Ser Lys Ser Ala His Ile Xaa Asn Tyr Arg Leu Gln Leu 25 30 35	
caa tca agg cag ggg	211
Gln Ser Arg Gln Gly	
40	
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                                                                        60
ttgacactcg ctccctgcca ccgcccgggc tccgtgccgc caagttttca ttttccacct
                                                                      120
tetetgeete cagteeecca geeeetggee gagagaaggg tettacegge egggattget
                                                                      180
ggaaacncaa gaggtggttt ttgtttttta aaacttctgt ttcttgggag ggggtgtggc
                                                                      240
ggggcagg atg agc aac tcc gtt cct ctg ctc tgt ttc tgg agc ctc tgc
                                                                      290
         Met Ser Asn Ser Val Pro Leu Leu Cys Phe Trp Ser Leu Cys
              -15
                                  -10
tat tgc ttt gct gcg ggg agc ccc gta cct ttt ggt cca gag gga cgg
                                                                      338
Tyr Cys Phe Ala Ala Gly Ser Pro Val Pro Phe Gly Pro Glu Gly Arg
ctg gaa gat aag ctc
                                                                      353
Leu Glu Asp Lys Leu
15
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                                                                       60
cagceggatt teccagecaa acgeagagag ag atg eee tqq ace ate ttq etc
                                                                      113
                                    Met Pro Trp Thr Ile Leu Leu
ttt gca gct ggc tcc ttg gcg atc cca gca cca tcc atc cgg gtg gtg
                                                                      161
Phe Ala Ala Gly Ser Leu Ala Ile Pro Ala Pro Ser Ile Arg Val Val
ccc ccg tac cca agc agc caa gag gac ccc atc cac atc gca tgc atg
                                                                      209
Pro Pro Tyr Pro Ser Ser Gln Glu Asp Pro Ile His Ile Ala Cys Met
                                         20
gcc gct ggg aac ttc ccg ggg gcg aat ttc aca ctg tat c
                                                                     249
Ala Ala Gly Asn Phe Pro Gly Ala Asn Phe Thr Leu Tyr
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PCT/IB99/00712 79

WO 99/53051 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 175..375 <221> sig\_peptide <222> 175..366 <223> Von Heijne matrix score 8.39999961853027 seq GFLFFGFLFPVFS/FP <400> 125

gtgctgcggc attcacgtga tctgcacggg cgcagatgta ggcaccggtc cgagtgcctg 60 contetation cognegating generating coordinates to the contest of t 120 cagettette caggtcagtg tgegggeett ceaegetgee ageggaacae tgga atg geg gaa ggg gaa cgg gtc tgc gcg tct gtk gtt ccc agc gct ctg cga 225 Ala Glu Gly Glu Arg Val Cys Ala Ser Val Val Pro Ser Ala Leu Arg' -60 -55 acg ctg aaa agg agg agc aac ctg tcc aga atc ccc gca gga cag gaa 273 Thr Leu Lys Arg Arg Ser Asn Leu Ser Arg Ile Pro Ala Gly Gln Glu -40 aag gag ggg aaa tot oga cat gtt got coo cot ttt ogo ttt tto cot 321 Lys Glu Gly Lys Ser Arg His Val Ala Pro Pro Phe Arg Phe Phe Pro -30 -25 ttt tcc ggt ttt ttg ttt ttt ggt ttt ctt ttt ccc gtc ttt tct ttc 369 Phe Ser Gly Phe Leu Phe Phe Gly Phe Leu Phe Pro Val Phe Ser Phe ccc tcc 375 Pro Ser

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<222> 223..435

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<222> 223..261

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<222> 404

<223> n=a, g, c or t

<400> 126

tcaataccca tgtgaacagt ttcgtggagg gttttaagta ttttccactg gctggctttg 60 ggtataagta cotttootto ttotgtogtt aaccacgcog aggggagaaa actatgcoco 120 cqtqaaaqtc cccactctgt ttcqgttggg gaatactgga gcttaacctc ttggagggqq 180 ttgttccata ccaagggtcc ttccgtaggt atttctaatg gg atg ttc tgc ctg 234 Met Phe Cys Leu

gca gca att tta gcc tca gca tct gcc caa cgg ttt cct tct gcc ttt Ala Ala Ile Leu Ala Ser Ala Ser Ala Gln Arg Phe Pro Ser Ala Phe - 5

282

score 8.39999961853027

80 tot cot toa cot tty yga tgg ott yrg car tgt aas act goo acc too 330 Ser Pro Ser Pro Phe Xaa Trp Leu Xaa Gln Cys Xaa Thr Ala Thr Ser 15 ttg ggt ttt trc act gtg tgy art aac tcc ata att tcc ttg tgg tat 378 Leu Gly Phe Xaa Thr Val Cys Xaa Asn Ser Ile Ile Ser Leu Trp Tyr . 30 tta ayg ggr gtt ccc cca gag gtt ang gaa ctc cct ttc ttt cca tat 426 Leu Xaa Gly Val Pro Pro Glu Val Xaa Glu Leu Pro Phe Phe Pro Tyr 45 50 437 tgc agc atg gg Cys Ser Met <210> 127 <211> 304 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 24..302 <221> sig\_peptide <222> 24..74 <223> Von Heijne matrix score 8.39999961853027 seq TLLLLLSEALALT/QT <400> 127 ctcaggactc agaggctggg atc atg gta gat gga acc ctc ctt tta ctc ctc 53 Met Val Asp Gly Thr Leu Leu Leu Leu Leu -15 teg gaa gee etg gee ett ace ear ace tgg geg gge tee eac tee tkr 101 Ser Glu Ala Leu Ala Leu Thr Gln Thr Trp Ala Gly Ser His Ser Xaa - 5 149 aag tat tte cae act tee gtg tee egg mee gge ege ggg gag eee ege Lys Tyr Phe His Thr Ser Val Ser Arg Xaa Gly Arg Gly Glu Pro Arg 15 20 ttc atc tct gtg ggc tac gtg gac gac acc cgg tca gag tat tgg gac 197 Phe Ile Ser Val Gly Tyr Val Asp Asp Thr Arg Ser Glu Tyr Trp Asp 30 cgg gag aca cgg agc gcc agg gac acc gca cag att ttc cga gtg aac 245 Arg Glu Thr Arg Ser Ala Arg Asp Thr Ala Gln Ile Phe Arg Val Asn 45 50 293 ctg cgg acg ctg cgc ggc tac tac aat cag agc gag gcc ggg tct cam Leu Arg Thr Leu Arg Gly Tyr Tyr Asn Gln Ser Glu Ala Gly Ser Xaa 60 65 304 acc ctg cag tg Thr Leu Gln 75 <210> 128 <211> 244 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 19..243 <221> sig\_peptide <222> 19..99 <223> Von Heijne matrix

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<221> misc_feature
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                                                                        60
ttgacactcg ctccctgcca ccgcccgggc tccgtgccgc caagttttca ttttccacct
                                                                       120
tetetgeete cagteececa geecetggee gagagaaggg tettacegge egggattget
                                                                       180
ggaaacncaa gaggtggttt ttgtttttta aaacttctgt ttcttgggag ggggtgtggc
                                                                       240
ggggcagg atg agc aac too gtt cot otg oto tgt tto tgg agc oto tgc
                                                                       290
         Met Ser Asn Ser Val Pro Leu Leu Cys Phe Trp Ser Leu Cys
                                  -10
tat tgc ttt gct gcg ggg agc ccc gta cct ttt ggt cca gag gga cgg
                                                                       338
Tyr Cys Phe Ala Ala Gly Ser Pro Val Pro Phe Gly Pro Glu Gly Arg
                                             10
ctg gaa gat aag ctc
                                                                       353
Leu Glu Asp Lys Leu
15
<210> 124
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      seq PWTILLFAAGSLA/IP
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                                                                       60
cageeggatt teccageeaa aegeagagag ag atg eee tgg ace ate ttg etc
                                                                      113
                                    Met Pro Trp Thr Ile Leu Leu
ttt gca gct ggc tcc ttg gcg atc cca gca cca tcc atc cgg gtg gtg
                                                                      161
Phe Ala Ala Gly Ser Leu Ala Ile Pro Ala Pro Ser Ile Arg Val Val
ccc ccg tac cca age age caa gag gae ccc ate cae ate gea tge atg
                                                                      209
Pro Pro Tyr Pro Ser Ser Gln Glu Asp Pro Ile His Ile Ala Cys Met
10
gcc gct ggg aac ttc ccg ggg gcg aat ttc aca ctq tat c
                                                                      249
Ala Ala Gly Asn Phe Pro Gly Ala Asn Phe Thr Leu Tyr
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<210> 125 < <211> 375

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                                                                        60
 ccctctgtcc ccgcggctgg gtctcgtctg ctccggttcc tgggctccta attcttggtc
                                                                       120
cagettette caggteagtg tgegggeett ceaegetgee ageggaacae tgga atg
                                                                       177
gcg gaa ggg gaa cgg gtc tgc gcg tct gtk gtt ccc agc gct ctg cga
                                                                       225
Ala Glu Gly Glu Arg Val Cys Ala Ser Val Val Pro Ser Ala Leu Arg
             -60
acg ctg aaa agg agg agc aac ctg tcc aga atc ccc gca gga cag gaa
                                                                       273
Thr Leu Lys Arg Arg Ser Asn Leu Ser Arg Ile Pro Ala Gly Gln Glu
                             -40
aag gag ggg aaa tot oga cat gtt got ooc oot tit ogo tit tio oot
                                                                       321
Lys Glu Gly Lys Ser Arg His Val Ala Pro Pro Phe Arg Phe Pro
                         -25
ttt tcc ggt ttt ttg ttt ttt ggt ttt ctt ttt ccc gtc ttt tct ttc
                                                                       369
Phe Ser Gly Phe Leu Phe Phe Gly Phe Leu Phe Pro Val Phe Ser Phe
-15
                                         - 5
ccc tcc
                                                                       375
Pro Ser
<210> 126
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<213> Homo sapiens
<220>
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<222> 223..435
<221> sig_peptide
<222> 223..261
<223> Von Heijne matrix
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      seq MFCLAAILASASA/QR
<221> misc_feature
<222> 404
<223> n=a, g, c or t
<400> 126
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                                                                       60
ggtataagta cctttccttc ttctgtcgtt aaccacgccg aggggagaaa actatgcccc
                                                                      120
cgtgaaagtc cccactctgt ttcggttggg gaatactgga gcttaacctc ttggaggggg
                                                                      180
ttgttccata ccaagggtcc ttccgtaggt atttctaatg gg atg ttc tgc ctg
                                                                      234
                                               Met Phe Cys Leu
gca gca att tta gcc tca gca tct gcc caa cgg ttt cct tct gcc ttt
                                                                      282
Ala Ala Ile Leu Ala Ser Ala Ser Ala Gln Arg Phe Pro Ser Ala Phe
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<221> sig\_peptide

<222> 24..74

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 seq TLLLLLSEALALT/QT

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 -5
 1
 5

 aag tat ttc cac act tcc gtg tcc cgg mcc ggc cgc ggg gag ccc cgc
 149

 Lys Tyr Phe His Thr Ser Val Ser Arg Xaa Gly Arg Gly Glu Pro Arg
 20
 25

 ttc atc tct gtg ggc tac gtg gac gac acc cgg tca gag tat tgg gac
 197

 Phe Ile Ser Val Gly Tyr Val Asp Asp Thr Arg Ser Glu Tyr Trp Asp
 197

101

245

30 35 40 cgg gag aca cgg agc gcc agg gac acc gca cag att ttc cga gtg aac Arg Glu Thr Arg Ser Ala Arg Asp Thr Ala Gln Ile Phe Arg Val Asn

45 50 55
ctg cgg acg ctg cgc ggc tac tac aat cag agc gag gcc ggg tct cam 293
Leu Arg Thr Leu Arg Gly Tyr Tyr Asn Gln Ser Glu Ala Gly Ser Xaa
60 65 70

acc ctg cag tg 304
Thr Leu Gln

75

<210> 128

<211> 244

<212> DNA

<213> Homo sapiens

<220>

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<222> 19..243

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 score 8.39999961853027

## seq LVLSLISLSIAWS/MV

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                                                                        51
                     Met Asn Phe Arg Gly Pro Gln Thr Phe Ser Leu
                                                  -20
 tca cac ago ctt gtg tta tcc cta atc agt ctc tcc att gca tgg tct
                                                                        99
Ser His Ser Leu Val Leu Ser Leu Ile Ser Leu Ser Ile Ala Trp Ser
                         -10
                                              -5
atg gtc gaa atg nbc act tct gca agc tac aar caa aag ttt gcc ctt.
                                                                       147
Met Val Glu Met Xaa Thr Ser Ala Ser Tyr Lys Gln Lys Phe Ala Leu
                                     10
aga atc cta gtt gtg cag ttg ccc aca tgg gtg gaa tgt cca gta aac
                                                                       195
Arg Ile Leu Val Val Gln Leu Pro Thr Trp Val Glu Cys Pro Val Asn
                                                      3.0
cac agg tgt gca cta ggg aga aag aat tgt tct att agg acc cag cca c
                                                                       244
His Arg Cys Ala Leu Gly Arg Lys Asn Cys Ser Ile Arg Thr Gln Pro
         35
                             40
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<212> DNA
<213> Homo sapiens
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<221> CDS
<222> 156..230
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ccttggtgtc atttgtggca gcctatagca ttagagcctt tgagaacaga tctttccaga
                                                                       120
ttctgcttaa gtccagggat tctgtgaccg cagaa atg act ggc atc tcc atc
                                                                       173
                                        Met Thr Gly Ile Ser Ile
tgc tcg tgc atc tgt ttg ttt ctt cct tca ttg att cac tca ttc ccc
                                                                       221
Cys Ser Cys Ile Cys Leu Phe Leu Pro Ser Leu Ile His Ser Phe Pro
                -10
ccg ccc tgc gg
                                                                       232
Pro Pro Cys
<210> 130
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<212> DNA

<213> Homo sapiens

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 score 8.30000019073486
 seq FLLLVAAPRWVQL/QE

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<222> 35172	•	
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score 8.19999980926514		
seq LVSLLMQPEGALG/EE		
•		
<400> 132		
	et Thr Pro Ala Leu Arg Cys -25	5
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Ala Phe Ala Leu Ala Ile Ala Gly Leu Val	Ser Leu Leu Met Gln Pro	
-20 -15	-10	
gag ggc gcc ctc ggc gag gag gct gca agt	gcc gca gcc cag ggc cgc 1	151
Glu Gly Ala Leu Gly Glu Glu Ala Ala Ser -5		
cag ttg gct gaa ctt agg ctc ca	10	
Gln Leu Ala Glu Leu Arg Leu	1	174
15		
	•	
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<211> 344		
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220	•	
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<221> sig peptide	. •	
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score 8.19999980926514		
seq LLLIFLSFPYTLC/IL		
400 122		
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ettttaactt caactgttct tttttcctgt aaatctt ettttctcct ac atg tct gga ctc ttc cca gt	aat tttcttttt tttctcccaa 1	20
Met Ser Gly Leu Phe Pro Va	of the state of th	71
-35	-30	
gat att gcc cag aac ata act tgc tct tcc		19
Asp Ile Ala Gln Asn Ile Thr Cys Ser Ser	Phe Ser Leu Leu Leu Tle	
-25 -20	-15 -10	
tt ctt tct ttc ccc tac acc ctc tgt ata	ctc tat aga gta aaa tca 2	67
Phe Leu Ser Phe Pro Tyr Thr Leu Cys Ile	Leu Tyr Arg Val Lys Ser	
-5	5	
at aca ccc acg gag tca ata act gcc ttt	aat cta aca att ggg wga 3	15
Tyr Thr Pro Thr Glu Ser Ile Thr Ala Phe	Asn Leu Thr Ile Gly Xaa	
10 15	20	
tc cca tat ctt taw wtt tcw acc ccg gg	34	44
he Pro Tyr Leu Xaa Xaa Ser Thr Pro		
25 30		
210: 124		
210> 134		
211> 244 212- DNA		
212> DNA		

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 <222> 128..244
 <221> sig_peptide
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                                                                         60
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                                                                        120
 tgtgcgg atg tgc agg gct gct tgt atc att aga atg gct gtt aga att
                                                                        169
         Met Cys Arg Ala Ala Cys Ile Ile Arg Met Ala Val Arg Ile
                     -30
                                          -25
 tca ttc ttt ctt tct tac cat gct ctg tct ctc tgc ctt tgt aca tgt
                                                                        217
 Ser Phe Phe Leu Ser Tyr His Ala Leu Ser Leu Cys Leu Cys Thr Cys
                 -15
                                     -10
 gcg ttt gca ttt ctc tcc ctc ctc ggg
                                                                        244
 Ala Phe Ala Phe Leu Ser Leu Leu Gly
 <210> 135
 <211> 217
 <212> DNA
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 <221> CDS
 <222> 40..216
<221> sig_peptide
<222> 40..90
<223> Von Heijne matrix
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      seq LLXALGFLXQVNP/XP
<400> 135
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                                                                        54
                                            Met Lys Phe Leu Leu
ctg gma gcc ctc gga ttc ctg amc cag gtg aat ccc arc cca att sma
                                                                       102
Leu Xaa Ala Leu Gly Phe Leu Xaa Gln Val Asn Pro Xaa Pro Ile Xaa
        -10
                             -5
ggd ggg tca aaa atg tgt gag twa cac ccc agg ata ctg cag gac atg
                                                                       150
Gly Gly Ser Lys Met Cys Glu Xaa His Pro Arg Ile Leu Gln Asp Met
                    10
                                         15
ttg cca ctg ggg gga gac agc att gtt cat gtg caa cgc tks cag aaa
                                                                       198
Leu Pro Leu Gly Gly Asp Ser Ile Val His Val Gln Arg Xaa Gln Lys
atg ctg cat cag yta ctc c
                                                                       217
Met Leu His Gln Leu Leu
            40,
<210> 136
<211> 428
<212> DNA
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<220>
<221> CDS
<222> 114..428
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<221> sig\_peptide

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<223> Von Heijne matrix
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                                                                       60
geettgacet etgeeteage eagtagegea gteteggeet egeegttacg gag atg
                                                                       116
gtg ccc tgg gtg cgg acg atg ggg cag aag ctg aag cag cgg ctg cga
                                                                       164
Val Pro Trp Val Arg Thr Met Gly Gln Lys Leu Lys Gln Arg Leu Arg
                         -35
                                             -30
ctg gac gtg gga cgc gag atc tgc cgc cag tac ccg ctg ttc tgc ttc
                                                                       212
Leu Asp Val Gly Arg Glu Ile Cys Arg Gln Tyr Pro Leu Phe Cys Phe
-25
                     -20
                                         -15
ctg ctg ctc tgt ctc agc gcc gcc tcc ctg ctt ctt aac agg tat att
                                                                       260
Leu Leu Leu Cys Leu Ser Ala Ala Ser Leu Leu Leu Asn Arg Tyr Ile
cat att tta atg atc ttc tgg tca ttt gtt gct gga gtt gtc aca ttt
                                                                       308
His Ile Leu Met Ile Phe Trp Ser Phe Val Ala Gly Val Val Thr Phe
                             15
tac tgc tca cta gga cct gat tct ctc tta cca aat ata ttc ttc aca
                                                                      356
Tyr Cys Ser Leu Gly Pro Asp Ser Leu Leu Pro Asn Ile Phe Phe Thr
                        30
ata aaa tac aaa ccc aag cag tta gga ctt cag gaa tta ttt cct caa
                                                                      404
Ile Lys Tyr Lys Pro Lys Gln Leu Gly Leu Gln Glu Leu Phe Pro Gln
                    45
40
                                         50
ggt cat agc tgt gct gtt tgt ggt
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Gly His Ser Cys Ala Val Cys Gly
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<222> 305..406
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                                                                       60
cagctgctcc acatttgtag cgaacacttt gactccaaag agaaggagga agacaaagac
                                                                      120
aagaaggaaa agaaagacaa ggacaagaag gaagcccctg ctgacatggg agcacatcag
                                                                      180
ggagtggctg ttctggggat tgcccttatt gctatggggg aggagattgg tgcagagatg
                                                                      240
gcattacgaa cctttggcca cttggtgagt atagcatgaa gaaaattgga atatactggt
                                                                      300
tttg atg gcc tgg ggt tcc cca ggg aag att ttt ctg atg ggt ttt ctt
                                                                      349
     Met Ala Trp Gly Ser Pro Gly Lys Ile Phe Leu Met Gly Phe Leu
ggt gga gag ctg gtc ttt ttg ctg tgc ctt ttc ttw ctt ttt ttc ttt
                                                                      397
Gly Glu Leu Val Phe Leu Cys Leu Phe Xaa Leu Phe Phe Phe
                -15
                                    -10
tot ttt ttg aag cgg agt ttt gct cta gag tgc aat g
                                                                      434
Ser Phe Leu Lys Arg Ser Phe Ala Leu Glu Cys Asn
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 <222> 310..357
 <223> Von Heijne matrix
       score 8.10000038146973
       seq SILLLLAPPLPSA/VS
<221> misc_feature
 <222> 189
 <223> n=a, g, c or t
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aaaagctctg taaacatata ataaatggaa ttccattgac attcaagcct tacgtatttc
                                                                        60
cagagettet tegaettate etgeeteece taetttaatt etgttaaagt agttgaacae
                                                                       120
cattettete ataatagtte teectesatt etteagtgat tyeettgtgt ttataggata
                                                                      180
aagtccacnt gttattttgg cagtcagttc aagatccaca aatcagtctt tacccttaca
                                                                      240
teettattte teactgetgt tetaatatag tetttatace agteaggetg gtetgtteae
                                                                      300
tatteetga atg ttt tte tee att ett ttg tta ttg gea eee eee eta eee
                                                                      351
          Met Phe Phe Ser Ile Leu Leu Leu Leu Ala Pro Pro Leu Pro
                                   -10
tot goa gtg tot ttg cta cot tto ttt tto tac tgt gtg cag gg
                                                                      395
Ser Ala Val Ser Leu Leu Pro Phe Phe Phe Tyr Cys Val Gln
<210> 139
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<222> 141..266
<221> sig_peptide
<222> 141..206
<223> Von Heijne matrix
      score 8.10000038146973
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caactotgot gittigtagg aagcoacatg gaggicatti acggitacta gitatottag
                                                                       60
tcagcttggg cagccattaa aaaataatac tgtagacgga gtggcccaaa cgagagaaat
                                                                      120
ttatttctta tagttttggc atg gta gat ttc atc ctg agg tct ctt ctc ttg
                                                                      173
                      Met Val Asp Phe Ile Leu Arg Ser Leu Leu Leu
                              -20
gtt tgt agt tgg ctg tca atc tcc ctg cat gct cac acg acc gct ttt
                                                                      221
Val Cys Ser Trp Leu Ser Ile Ser Leu His Ala His Thr Thr Ala Phe
                        -5
tgt aca tac agt aag aaa ata cac act gtc atg tca ttt ttt tgt aa
                                                                      268
Cys Thr Tyr Ser Lys Lys Ile His Thr Val Met Ser Phe Phe Cys
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<222> 93..170
<221> sig_peptide
<222> 93..140
<223> Von Heijne matrix
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ttttgactga tatcaaattc taggtggacc gagattttct ttcagtcttt caaagatatt
                                                                       60
actitattgc cttctatctt gcatagtttc tg atg aga agt ctg ttg tat ttc
                                                                      113
                                    Met Arg Ser Leu Leu Tyr Phe
                                         -15
tta tgt gtt tct tca tat gta aca tct ttt ttc ttt ttt ttt ttt ttt
                                                                       161
Leu Cys Val Ser Ser Tyr Val Thr Ser Phe Phe Phe Phe Phe Phe Phe
                -5
                                     1
ttt ttt ttt
                                                                      170
Phe Phe Phe
        10
<210> 141
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<222> 192..395
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      seq FISFLCLIALAGT/SS
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                                                                       60
tgtatccgga aactttgttg aattatttta tcagttctag gagctttttg gaggagtctt
                                                                      120
tagggttctc taggtataca atcatatcat cagcaaacag tgacaattcg acttcctctt
                                                                      180
tatggatttg t atg ccc ttt att tct ttc ctt tgt ctg att gct ctg gct
                                                                      230
             Met Pro Phe Ile Ser Phe Leu Cys Leu Ile Ala Leu Ala
                                 -10
ggg act tee agt act atg ttg aga agt get etg get ggg act tee agt
                                                                      278
Gly Thr Ser Ser Thr Met Leu Arg Ser Ala Leu Ala Gly Thr Ser Ser
act atg tkg arg aga agt ggt gam agt ggg wat cct kgh ctk gty cma
                                                                      326
Thr Met Xaa Xaa Arg Ser Gly Xaa Ser Gly Xaa Pro Xaa Leu Val Xaa
gtc ctm aga ggg aat gct ttc agc ttt ttc cca ttc agt ctg atg twg
                                                                      374
Val Leu Arg Gly Asn Ala Phe Ser Phe Phe Pro Phe Ser Leu Met Xaa
gct atg ggt tgt cat aga tgg c
                                                                      396
Ala Met Gly Cys His Arg Trp
           50
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<210> 142 <211> 357

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 tgttctgcaa taggcggctt agagggaggg gctttttcgc ctatacctac tgtagcttct
                                                                      120
 ccacgtatgg accetaaagg ctactgetge tactaegggg ctagacagtt actgteteag
 ctctaggatg tgcgttcttc cactagaagc tcttctgagg gaggtaatta aaaaacagtg
                                                                       240
 gaatggaaaa acagtgctgt agtcatcctg taatatgctc cttgtcaaca a atg tat
                                                                       297
                                                           Met Tyr
 aca ttc ctg cta ggt gcc ata ttc att gct tta agc tca agt cgc atc
                                                                       345
 Thr Phe Leu Leu Gly Ala Ile Phe Ile Ala Leu Ser Ser Arg Ile
 tta cta gtg aag
                                                                       357
 Leu Leu Val Lys
         5
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tgtgtgtgtg tgtgtctgcg tgtgt atg tgt ttg tgt ccc tgc tgg gat gtg
                                                                        52
                             Met Cys Leu Cys Pro Cys Trp Asp Val
                                     -40
                                                         -35
 ttt act gtg ttt gtg tgt gtc tct gtg tgt gtg tct gtg tct gtc cct
                                                                       100
 Phe Thr Val Phe Val Cys Val Ser Val Ser Val Ser Val Pro
                                 -25
 gtc ggg atg tat tta gtg tgt gtg tgt gtg tgt gtg tgt gtg tgt stc
                                                                       148
 Val Gly Met Tyr Leu Val Cys Val Cys Val Cys Val Cys Xaa
                             -10
 tgc gyg cgt gg
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 Cys Xaa Arg
     1
<210> 144
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<221> CDS

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aaaataaggt atctggcaaa agaatatatg aaagagtatg aagaactctc cttgaaagct
                                                                       60
gtggcccca ttggccatgg ctgcagagcc gatgtcccgg ccaatccagg cgggatccc
                                                                      120
ttgaagcmgg knsmwhbtcy kragscwknc cmabtctccg ggggcaastc ttttcccttc
                                                                      180
cctgtgaccc kcttcggaca gttgaccatc tcaacaccta gtggttaaaa agaagagcat
                                                                      240
ggacggcctg gggcctgcac tggctgtgct gggagtttgt c atg ttg ata gct aag
                                                                      296
                                               Met Leu Ile Ala Lys
cag gcc cag ccc caa ggc ctc act gcc atc tgc ttc cct ctc aca cct
                                                                      344
Gln Ala Gln Pro Gln Gly Leu Thr Ala Ile Cys Phe Pro Leu Thr Pro
                -25
                                     -20
ctc ttc tcc ctc ctc atg ctc act cag agc ccc ctt gca ggt cag gaa
                                                                      392
Leu Phe Ser Leu Leu Met Leu Thr Gln Ser Pro Leu Ala Gly Gln Glu
            -10
                                ~ 5
gga aga gaa gga ggg aaa gaa cgg tac ttg ttg gtg att ca
                                                                      433
Gly Arg Glu Gly Gly Lys Glu Arg Tyr Leu Leu Val Ile
                        10
<210> 145
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<222> 15..200
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aatacgccag gaac atg cta agg acc tgg agc tct cta ccc tgg acc cgt
                                                                       50
                Met Leu Arg Thr Trp Ser Ser Leu Pro Trp Thr Arg
                    -25
                                        -20
ttt cgg gtt tgc ttg ctc tct ctc tct ctc ttt ctc tgg gct aat cgt
                                                                       98
Phe Arg Val Cys Leu Leu Ser Leu Ser Leu Phe Leu Trp Ala Asn Arg
                                    -5
tta gag gac agt cgc tcc tgc caa cct aat ccc atg agc ctg act acc
                                                                      146
Leu Glu Asp Ser Arg Ser Cys Gln Pro Asn Pro Met Ser Leu Thr Thr
                            10
ttg ccg ggc cac agg ctc aaa gaa gca gtg tgg ctg cca gca ccc tca
                                                                      194
Leu Pro Gly His Arg Leu Lys Glu Ala Val Trp Leu Pro Ala Pro Ser
                        25
                                            30
ctt ggg
                                                                      200
Leu Gly
35
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aacaccccag cccaagttca tccccggtcc cttggcagca gtgcgcatcc acaaagccag
                                                                       60
eggeacaatt taattactg atg gee eet tte eta ega eag gtg gat rtg tgg
                                                                       112
                     Met Ala Pro Phe Leu Arg Gln Val Asp Xaa Trp
                                      -25
gga gca cag gcc ggt ctg gtg gtb gsm tgg tta cta cca tgs caa tgc
                                                                       160
Gly Ala Gln Ala Gly Leu Val Val Xaa Trp Leu Leu Pro Xaa Gln Cys
            -15
                                -10
age tgt gaa ega tea gag caa tat etg age ace tgt etc eea eag cae
                                                                       208
Ser Cys Glu Arg Ser Glu Gln Tyr Leu Ser Thr Cys Leu Pro Gln His
tca ago ato aag cag tog tgo ato aag cat coa goa ggo cog ato coc
                                                                       256
Ser Ser Ile Lys Gln Ser Cys Ile Lys His Pro Ala Gly Pro Ile Pro
                    20
                                        25
gca ggc cac cta cag gga aag gcc aca gct gcg ccc ctg gg
                                                                      297
Ala Gly His Leu Gln Gly Lys Ala Thr Ala Ala Pro Leu
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      seg WLFLVAILKGVRC/EV
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agctctgaga gaggagccca gccctgggat cttcaggtgt tttcactcgg tgatcaggac
                                                                       60
tgcacagaga gaactcacc atg gag ttt ggg ctg aag tgg ctt ttt ctt gtg
                                                                      112
                    Met Glu Phe Gly Leu Lys Trp Leu Phe Leu Val
                                     -15
gca att tta aaa ggt gtc cgg tgt gaa gtg aag ctg gtg gag tct ggg
                                                                      160
Ala Ile Leu Lys Gly Val Arg Cys Glu Val Lys Leu Val Glu Ser Gly
gga ggc ctg gtg cag ccg ggg ggg tcc ctg aga ctc tcc tgt gta gga
                                                                      208
Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Val Gly
                       15
tot gga tto gto tto gat aaa tat ggo ata agt tgg gtg cgc cag gca
                                                                      256
Ser Gly Phe Val Phe Asp Lys Tyr Gly Ile Ser Trp Val Arg Gln Ala
                   30
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seq LLLFPLSLLFTLG/FL

cca gga aag ggc cta cag tgg gtc gcg ggg atc ggt ggc ggg gg 300 Pro Gly Lys Gly Leu Gln Trp Val Ala Gly Ile Gly Gly <210> 148 <211> 405 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 21..404 <221> sig\_peptide <222> 21..68 <223> Von Heijne matrix score 7.90000009536743 seq AMLVLVVSPWSAA/RG <400> 148 geggtettee ageagggaaa atg geg etg gee atg etg gte ttg gtg gtt teg Met Ala Leu Ala Met Leu Val Leu Val Val Ser -15 -10 ccg tgg tct gcg gcc cgg gga gtg ctt cga aac tac tgg gag cga ctg 101 Pro Trp Ser Ala Ala Arg Gly Val Leu Arg Asn Tyr Trp Glu Arg Leu cta cgg aag ctt ccg cag agc cgg ccg ggc ttt ccc agt cct ccg tgg 149 Leu Arg Lys Leu Pro Gln Ser Arg Pro Gly Phe Pro Ser Pro Pro Trp 15 20 gga cca gca tta gca gta cag ggc cca gcc atg ttt aca gag cca gca 197 Gly Pro Ala Leu Ala Val Gln Gly Pro Ala Met Phe Thr Glu Pro Ala 30 35 aat gat acc agt gga agt aaa gag aat too ago ott ttg gac agt atc 245 Asn Asp Thr Ser Gly Ser Lys Glu Asn Ser Ser Leu Leu Asp Ser Ile . 50 55 ttt tgg atg gca gct ccc aaa aat aga cgc acc att gaa gtt aac cgg 293 Phe Trp Met Ala Ala Pro Lys Asn Arg Arg Thr Ile Glu Val Asn Arg 65 70 tot agg aga aga aat ccg cag aag ctt att aaa gtt aag aac aac ata 341 Cys Arg Arg Arg Asn Pro Gln Lys Leu Ile Lys Val Lys Asn Asn Ile 85 gac gtt tgt cct gaa tgt ggt cac ctg aaa cag aaa srt gtc ctt tgt 389 Asp Val Cys Pro Glu Cys Gly His Leu Lys Gln Lys Xaa Val Leu Cys 100 gct act gct atg aaa a 405 Ala Thr Ala Met Lys 110 <210> 149 <211> 146 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 56..145 <221> sig\_peptide <222> 56..115 <223> Von Heijne matrix score 7.80000019073486

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 ttt ttc tac tca cac ttt tta ctt ctt ttt ccc ctc tcg tta ctt ttc
                                                                     106
 Phe Phe Tyr Ser His Phe Leu Leu Leu Phe Pro Leu Ser Leu Leu Phe
                 -15
                                     -10
 146
 Thr Leu Gly Phe Leu Phe Val Phe Phe Phe Phe Phe
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 caagaagacg gaccccgagt gggaggcaga gagacaagag gtgg atg aag cag agc
                                                                     116
                                                 Met Lys Gln Ser.
 aag cgt gas atg gtg aag aga aga cgg agc ccc gcg ctg gga gag gaa
                                                                     164
 Lys Arg Xaa Met Val Lys Arg Arg Arg Ser Pro Ala Leu Gly Glu Glu
       -40
                            -35
 ege tte agt eeg agt tee att etg eac eea agg ete eec ttg gte ete
 Arg Phe Ser Pro Ser Ser Ile Leu His Pro Arg Leu Pro Leu Val Leu
                        -20
                                            -15
 ctg gga acc agg gtg ccc ctt agt ggt ggt ggc cca gga gaa ccc gac
                                                                     260
Leu Gly Thr Arg Val Pro Leu Ser Gly Gly Gly Pro Gly Glu Pro Asp
                    -5
caa ggc agg agc gcc ccc tcc tgg aag agc ctc gct tca acg cat mat
                                                                     308
Gln Gly Arg Ser Ala Pro Ser Trp Lys Ser Leu Ala Ser Thr His Xaa
            10
                               15
cat tee egg eeg gea gea ggg geg aeg eea gea agg eet geg aet eag
                                                                     356
His Ser Arg Pro Ala Ala Gly Ala Thr Pro Ala Arg Pro Ala Thr Gln
                            30
age cag ett gge ceg tte gee ceg eee ett eee ggt gte ege eee gee
                                                                     404
Ser Gln Leu Gly Pro Phe Ala Pro Pro Leu Pro Gly Val Arg Pro Ala
                        45
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cca t
                                                                     408
Pro
55
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gcc cta cac ggg gac tct Ala Leu His Gly Asp Ser 1	agg gtg gaa tg Arg Val Glu Cy 5	t agc aaa gcc c	at cca cca 216 is Pro Pro
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15

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-35 -30 -25 -20 ctc ttc cag ttt tct ctg cth mtc ttg gga gag ggt ctc acc ttt ctt 325 Leu Phe Gln Phe Ser Leu Leu Xaa Leu Gly Glu Gly Leu Thr Phe Leu -15 -10 tgc ctc tgc cag gta atg acg aat aan atg caa ctg ctg ttc ttg agt 373 Cys Leu Cys Gln Val Met Thr Asn Xaa Met Gln Leu Leu Phe Leu Ser ggg gta gtc tgt ggg 388 Gly Val Val Cys Gly 15 <210> 162 <211> 235 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 172..234 <221> sig peptide <222> 172..210 <223> Von Heijne matrix score 7.5 seq MAPLLLSLSCSFS/CH <400> 162 cccctccaaa tctcatgttg agatttgatc cctaatgttg gagatggggc ctggtgggag 60 atattcggat catgagggca gatccctcac taatggcctg gtgccctccc tgtggaaatg 120 agtaagttct cactettttg gttcacetga gagetgtttg tttaaaagag c atg gca 177 Met Ala ccc ctc ctt ctc tct ctg tct tgc tcc ttt tct tgc cat gtg aca ctc 225 Pro Leu Leu Ser Leu Ser Cys Ser Phe Ser Cys His Val Thr Leu ctg ccc cgg g 235 Leu Pro Arg <210> 163 <211> 240 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 99..239 <221> sig\_peptide <222> 99..158 <223> Von Heijne matrix score 7.5 seq LLWVLLLNLGPRA/AG <400> 163 aaaacgaccc ggtgggtcta cagcggaagg gagggagcga aggtaggagg cagggcttgc 60 ctcactggcc accctcccaa ccccaagagc ccagcccc atg gtc ccc gcc gcs 116 Met Val Pro Ala Ala Gly -20 gcg ctg ctg tgg gtc ctg ctg ctg aat ctg ggt ccc cgg gcg gcg ggg 164 Ala Leu Leu Trp Val Leu Leu Leu Asn Leu Gly Pro Arg Ala Ala Gly -10 ~ 5 gcc caa ggc ctg acc cag act ccg acc gaa atg cag cgg gtc agt tta 212 Ala Gln Gly Leu Thr Gln Thr Pro Thr Glu Met Gln Arg Val Ser Leu

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                     Met Val Phe Trp Glu Ile Ser Val Gln Ile Ile
                                     -20
ctg atc tct gaa ctc ctg ctg ttg agg tca gtc act tca cac aat acc
                                                                      100
Leu Ile Ser Glu Leu Leu Leu Arg Ser Val Thr Ser His Asn Thr
            -10
                                 -5
atg atg aga gct tta tca agc cag atg ctt agt cag agc ttt cca aga
                                                                      148
Met Met Arg Ala Leu Ser Ser Gln Met Leu Ser Gln Ser Phe Pro Arg
                        10
                                             15
ccc agc ttt ggt ttt atc agc aaa atc cat cct tcc cac ccc ccc aa
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Pro Ser Phe Gly Phe Ile Ser Lys Ile His Pro Ser His Pro Pro
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                                         -50
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                                                                     1.02
Met Phe Ile Val Val Met Val Gln Ile Cys Gly Arg Asn Gly Lys Arg
               -40
                                    -35
age aac egg acc etg aga gaa gaa gtg tta agg aac etg ege agt gtg
                                                                     150
Ser Asn Arg Thr Leu Arg Glu Glu Val Leu Arg Asn Leu Arg Ser Val
           -25
                                -20
                                                    -15
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gtt ag Val Se	gc ttg er Leu -10	acc Thr	ttt Phe	ctg Leu	ttg Leu	ggc Gly -5	atg Met	aca	tgg	ggt Gly	ttt Phe	gca Ala	ttc Phe	ttt Phe	198
gcc to Ala Tr 5	gg gga rp Gly	ccc Pro	tta Leu	aat Asn 10	atc Ile	ccc	ttc Phe	atg Met	tac Tyr 15	ctc Leu	ttc	tcc Ser	atc Ile	ttc Phe 20	246
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Phe Le		Leu	Leu	Xaa	Xaa 5	Leu	Ile	Val	Ala	gtg Val 1	Thr	Ser	Leu	Gln 5	101
Cys Il	a aca e Thr	Cys	His 10	Leu	Arg	Thr	Arg	Thr. 15	Asp	Arg	Cys	Arg	Arg 20	Gly	149
Phe Gl		Cys 25	act Thr	gct Ala	cag Gln	Lys	ggc Gly 30	gag Glu	gca Ala	tgc Cys	atg Met	ctc Leu 35	tta Leu	agg Arg	197
	s Gln 40														209
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atg ga Met Gl -3	g tct g u Ser V 0	gtc a /al :	acc t Thr I	Leu	tca ( Ser :	cca ( Pro )	gcc Ala	cca Pro	Val	ttc Phe -20	ccc	gtc Val	cct Pro	gca Ala	103
						•									

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101 car ctc ctt tta ctg aca tcc cat ttt cta ggc gag tcc ctt ggt gga Gln Leu Leu Leu Thr Ser His Phe Leu Gly Glu Ser Leu Gly Gly -10 -15 ggc aca ctg ctt gtc cca ctc ctc ccc cca ggg 184 Gly Thr Leu Leu Val Pro Leu Leu Pro Pro Gly <210> 168 <211> 218 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 97..216 <221> sig\_peptide <222> 97..177 <223> Von Heijne matrix score 7.40000009536743 seq ILLLTICAAGIXG/TR <400> 168 cettecetee gegeacagge tgeeggetea eegettgeta atggeageeg gggteteeet 60 gggacagcaa gacctccgct caggcccctc tttcga atg ckc cam gcm ctc ctg 114 Met Xaa Xaa Ala Leu Leu -25 cga tot aga atg att cag ggc agg atc ctg ctc ctg acc atc tgc gct 162 Arg Ser Arg Met Ile Gln Gly Arg Ile Leu Leu Leu Thr Ile Cys Ala -15 -10 gcc ggc att rgt ggg act cgt cag ttt ggc tat aac ctc tct atc atc 210 Ala Gly Ile Xaa Gly Thr Arg Gln Phe Gly Tyr Asn Leu Ser Ile Ile -5 aat gac cc 218 Asn Asp <210> 169 <211> 480 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 317..478 <221> sig\_peptide <222> 317..457 <223> Von Heijne matrix score 7.40000009536743 seq SCLFSXAWLXCXC/HG <400> 169 gtotogtggg ctggtcccca gcggctccct ccccgaacag ctgctgctcc agggaggaag eggegyrrgt gmtgtecage tteeeggtge tgaaaacegg agggetegte atecaceact 120 accatqtaaq ggccatgaga agggctcatc ctggcgcasg cggacatgga qqaqqactta 180 ttccagctaa ggcagctgcc ggttgtgaaa ttccgtcgca caggcgagag tqcaaqqtca 240 qaqqacqaca cggcttcagg agaqcatqaa qtccaqattg aaqqggtcca cqtqqqccta 300 gaggetgtgg agetgg atg atg ggg cak etg tge eea agg agt ttg eea ate 352 Met Met Gly Xaa Leu Cys Pro Arg Ser Leu Pro Ile -45 -40 cca ccg atg ata ctt tca tgg tgg aag atg cag tgg aag cca ttg gct 400 Pro Pro Met Ile Leu Ser Trp Trp Lys Met Gln Trp Lys Pro Leu Ala -35 -30 -25

103

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                                       -10
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                                                                         480
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                                                                        170
                 Met Gly Leu Leu Gln Leu Leu Ala Phe Ser Phe Leu
                  -15
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                                                                        218
 Gly Asn Ser Val Glu Thr Val Arg Gly Gly Gly Arg Thr Trp Ala Trp
             1
 gga agg aaa acc caa aag ctg ctt gct cac ctt cgt ggg atc ctg ggg
                                                                        266
 Gly Arg Lys Thr Gln Lys Leu Leu Ala His Leu Arg Gly Ile Leu Gly
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                         20
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                               Met Leu Val Leu Val His Ser Ser Leu
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age aag ace ttg tet cag aaa aaa aaa aag tte aca aas eec ace agg g
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                                                                       111
               Met Ser Phe Ser Ser Ala Leu Ile Leu Val Ile Ser Cys
                               -15
 ctt ctg cta gct ttt gaa tgt gtt tgc tct tgc ttt tct ggt tct ttt
                                                                       159
Leu Leu Leu Ala Phe Glu Cys Val Cys Ser Cys Phe Ser Gly Ser Phe
aat tgt gat gtt agg gtg tca att tcg gat ctt tcc tgc ttt ctc ttg
                                                                       207
Asn Cys Asp Val Arg Val Ser Ile Ser Asp Leu Ser Cys Phe Leu Leu
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tgg ggc aag gg
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Trp Gly Lys
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tcaactcatc aaagtcattc tccatccagc tttgttccat tgctggtgag gaactgtgtt
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ccttcggagg aggagaggtg ctctgctttt ttgagtttcc agtttttctg ctctgtttt
                                                                      240
tececatett tgtggtttta tetaettttg gtetttgatg etggtgatgt acag atg
                                                                      297
ggt ttt tgg tgt gga tgt cct ttc tgt ttg twa gtt ttc ctt cta aca
                                                                      345
Gly Phe Trp Cys Gly Cys Pro Phe Cys Leu Xaa Val Phe Leu Leu Thr
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                        -15
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Met Val Leu Leu Ser Leu Ser Leu Trp Gly Ile Ser Thr Leu Ser Ser
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                                         - 5
aca aca att gaa cta att tac acc ccc atc ggg
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Thr Thr Ile Glu Leu Ile Tyr Thr Pro Ile Gly
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                                          Met Ala Ser Leu Leu Ser
                                          - 25
ggc ttt act agc ttc tgt ctt ttg cac gtt cac tct ttc ctc cct cca
                                                                       103
Gly Phe Thr Ser Phe Cys Leu Leu His Val His Ser Phe Leu Pro Pro
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                                     -10
gtg ttt tcc acc cag aat g
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Val Phe Ser Thr Gln Asn
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<210> 178

<211> 222

<212> DNA

<213> Homo sapiens

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 <222> 30..221
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<222> 30..95
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acgtcggacc cggaggccct gaatgcccc atg cgc acc cca cag ctc gcg ctc
                                                                        53
                                 Met Arg Thr Pro Gln Leu Ala Leu
                                          -20
ctg caa gtg ttc ttt ctg gtg ttc ccc gat ggc gtc cgg cct cag ccc
                                                                       101
Leu Gln Val Phe Phe Leu Val Phe Pro Asp Gly Val Arg Pro Gln Pro
                 -10
                                     -5
tet tee tee cea tea ggg gea gtg eec acg tet ttg gag etg cag ega
Ser Ser Ser Pro Ser Gly Ala Val Pro Thr Ser Leu Glu Leu Gln Arg
        5
                             10
                                                 15
ggg acg gat ggc gga acc ctc cag tcc cct tca gag gcg act gca act
                                                                       197
Gly Thr Asp Gly Gly Thr Leu Gln Ser Pro Ser Glu Ala Thr Ala Thr
                         25
                                             30
cgc ccg gcc gtg ccc gga ctc cgg g
                                                                       222
Arg Pro Ala Val Pro Gly Leu Arg
35
                     40
<210> 179
<211> 171
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<222> 33..95
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cettttgcct tcaacetteg ageogecaeg ta atg cca egt eec ege gea tge
                                                                        53
                                     Met Pro Arg Pro Arg Ala Cys
                                         -20
                                                              -15
gca tet tgg eeg etg etg geg get gtt tee ggg ett aga ggg etg gag
                                                                       101
Ala Ser Trp Pro Leu Leu Ala Ala Val Ser Gly Leu Arg Gly Leu Glu
                                     -5
tgg ccg ccg agt tgg agg cgg gtg gtg gca gca gta gga gtg tgt aga
                                                                       149
Trp Pro Pro Ser Trp Arg Arg Val Val Ala Ala Val Gly Val Cys Arg
gtg cgg gat tgg ggg ccc cgg g
                                                                       171
Val Arg Asp Trp Gly Pro Arg
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<210> 180
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<222> 177..227
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tgtaattttc cttgccaaaa agcttagttt catcttttat aaatatccta taatgccaag
ttgattgcat ggtcagagtg aatctgtgct gtacccawat tcagtagcct tctcctatcc
                                                                    120
aat gga att ttc ttg ctc ttg atc tct gtc tta aca gtg att tgg ttt
                                                                   227
Asn Gly Ile Phe Leu Leu Leu Ile Ser Val Leu Thr Val Ile Trp Phe
    -15
                        -10
tgg aag aca cac ccg ggg
                                                                   245
Trp Lys Thr His Pro Gly
<210> 181
<211> 241
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<222> 160..213
<223> Von Heijne matrix
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<400> 181
gttgactttt ctctctgctg aggcagaaaa atgcttccat agtccatgca gcaatgttta
aaacaaggga tttcgttccc ccctcvcctt ttgtgtaggc tggttaataa actctgtgtt
                                                                   120
tywtagcatt gtcgtgaawa ttcagagtgc tccctgcga atg gtt ttc cta gta
                                                                   174
                                          Met Val Phe Leu Val
ket etg ttg tgt ate att ket ett tat ttg att egt ggt tet gag tgg
                                                                   222
Xaa Leu Leu Cys Ile Ile Xaa Leu Tyr Leu Ile Arg Gly Ser Glu Trp
            -10
                               -5
amo cta cca ccg aac tgg g
                                                                   241
Xaa Leu Pro Pro Asn Trp
   5
<210> 182
<211> 263
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 103..261
<221> sig peptide
<222> 103..156
<223> Von Heijne matrix
     score 7.19999980926514
     seq LFFLLRIALASWA/LF
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<400> 182

gggttatcta acctgttcca ttgttccgtg tatcagtttc tgtaccgata ccatgctgtt ttggttactg tagtcttgta gtatagttta aagtcagata gc atg atg act cta  Met Met Thr Leu  -15	60 114
gct ttg ttc ttt ttg ctt agg att gct ttg gct agt tgg gct ctc ttt Ala Leu Phe Phe Leu Leu Arg Ile Ala Leu Ala Ser Trp Ala Leu Phe -10 -5	162
tgg atc cat atg aat ttt aga aga gct ttt ttc cac tta cgg tgg ttt Trp Ile His Met Asn Phe Arg Arg Ala Phe Phe His Leu Arg Trp Phe 5 10 15	210
gat atc aat agc act gaa tct gta aat tgc ttt ggg cag tat ggc cta Asp Ile Asn Ser Thr Glu Ser Val Asn Cys Phe Gly Gln Tyr Gly Leu 20 25 30	258
gcg gg Ala 35	263
<210> 183	
<211> 170 <212> DNA	
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score 7.09999990463257 seq SLLVFCLNDLSNA/VX	· .
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ttccatgtgg agatgrraag aatatatatt ctgtggttat tgggtagagt gttctatag atg tct att agg tct aat tgg tct agt gtc gaa tct aag tct aga att	59
Met Ser Ile Arg Ser Asn Trp Ser Ser Val Glu Ser Lys Ser Arg Ile  -25  -20  -15	107
Ser Leu Leu Val Phe Cys Leu Asn Asp Leu Ser Asn Ala Val Xaa Xaa	155
ggm att gaa rtc ccc Gly Ile Glu Xaa Pro 5	170
<210> 184	
<211> 443	
<pre>&lt;212&gt; DNA &lt;213&gt; Homo sapiens</pre>	
:220>	÷
221> CDS	
222> 83442	
:221> sig_peptide :222> 83130	
score 7.0999999463257 seq IPLFLGVLAYCTG/SV	
400> 184	
etttccagca aggggataag agaggcctgg aagaacctgc ccagcctggg cctcaggaag agcatcgga ggtgcctcag cc atg gca tgg atc cct ctc ttc ctc ggc gtc	60 112

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-15
 ctt gct tac tgc aca gga tcc gtg gcc tcc tat gag ctg act cac cca
                                                                        160
 Leu Ala Tyr Cys Thr Gly Ser Val Ala Ser Tyr Glu Leu Thr His Pro
 ccc tca gtg tcc gtg tcc cca gga cag aca gcc agc atc acc tgc tct
                                                                       208
 Pro Ser Val Ser Val Ser Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser
                  15
                                      20
                                                          25
 gga gat aaa ttg ggg gat aaa tat gct tgc tgg tat cag cag aag cca
                                                                       256
 Gly Asp Lys Leu Gly Asp Lys Tyr Ala Cys Trp Tyr Gln Gln Lys Pro
 ggc cag tcc cct gtg ctg gtc atc tat caa gat agc aag cgg ccc tca
                                                                       304
 Gly Gln Ser Pro Val Leu Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser
         45
                             50
                                                  55
 ggg atc cct gag cga ttc tct ggc tcc aac tct ggg aac aca gcc act
                                                                       352
 Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr
                         65
                                              70
 ctg acc atc agc ggg acc cag gct atg gat gag gct gac tat tac tgt
                                                                       400
 Leu Thr Ile Ser Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys
 75
                     80
                                         85
 cag gcg tgg gac agc agc act gtg gta ttc ggc gga ggg acc a
                                                                       443
 Gln Ala Trp Asp Ser Ser Thr Val Val Phe Gly Gly Gly Thr
                 95
 <210> 185
 <211> 427
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<222> 332..427
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<222> 332..418
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                                                                        60
atgttaccct gtgtgagaca aaacaaaaca gtgactagaa ccctccttgt gggctaaatt
                                                                       120
tgagtttgct tcttcataat gttttaaatg cttcacaaac atttttcttt ggtatattga
                                                                       180
gcaaaatgaa ttgaagtata tttactgagt gatgattatt gaggaaaaac tcaaagatct
                                                                       240
gctgtaagca ctagagttga aggactagcc caacagctcc tcaggcacct ttgggtatat
                                                                       300
tgagttgccc cccctgactt tgaacacatc t atg gtc tgt gtc atc ttc aaa
                                                                       352
                                   Met Val Cys Val Ile Phe Lys
gag ctc atg gaa ttt gaa ttc cct ggg ttt tgt ttt tgh ctt tgt ttt
                                                                       400
Glu Leu Met Glu Phe Glu Phe Pro Gly Phe Cys Phe Xaa Leu Cys Phe
        -20
gga cgg agc tcg ctc tgt tgc cga rac
                                                                      427
Gly Arg Ser Ser Leu Cys Cys Arg Xaa
<210> 186
<211> 365
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 130..363
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<221> sig\_peptide

<222> 130..219 <223> Von Heijne matrix score 7.09999990463257 seq SCLALXTLAVVYA/AL <400> 186 aacgagtett tgggaacgtg gtccacccag ggatgtaaaa etgtgettae egatgeatee 60 catacgaaat gcttatgtga tcgtctctct accttcgcca ttttggctca gcaacctaga 120 gaaataatc atg gaa too tot ggc aca cot toa gtt acc cta ata gta ggc 171 Met Glu Ser Ser Gly Thr Pro Ser Val Thr Leu Ile Val Gly -25 agt ggt ctt tct tgc ttg gcc ttg atb acc cta gca gtt gtc tat gca 219 Ser Gly Leu Ser Cys Leu Ala Leu Xaa Thr Leu Ala Val Val Tyr Ala -15 -10 gca tta tgg mgg tac ata cgc tct gag aga tcc ata ata cta att aac 267 Ala Leu Trp Arg Tyr Ile Arg Ser Glu Arg Ser Ile Ile Leu Ile Asn 10 ttc tgc ctg tct atc atc tca tcc aat atc ctc ata ctg gtt gga cag 315 Phe Cys Leu Ser Ile Ile Ser Ser Asn Ile Leu Ile Leu Val Gly Gln act cag aca cat aat aaa gag tat ctg cac aac cac tqc att ttt 363 Thr Gln Thr His Asn Lys Glu Tyr Leu His Asn His His Cys Ile Phe 40 gc 365 <210> 187 <211> 260 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 86..259 <221> sig\_peptide <222> 86..178 <223> Von Heijne matrix score 7.09999990463257 seq LXFLASSFCFGEA/DS <221> misc\_feature <222> 143 <223> n=a, g, c or t <400> 187 ttttggaaca gggtaggcat tttgtttatt gtttgcttgc ttctaggtgt tttcgccatc 60 agggtgtatt ggaggetgae aetta atg ggt gtg tgt tge gee eag aac tge 112 Met Gly Val Cys Cys Ala Gln Asn Cys -30 tcg gtg tcg ggg ktc waa agr aat gcg ctg ntg ttc ttg gct tca agt 160 Ser Val Ser Gly Xaa Xaa Arg Asn Ala Leu Xaa Phe Leu Ala Ser Ser -15 tto tgo ttt 99a 9aa goa gat toa gga agt agg tgt tgo tta aaa ata 208 Phe Cys Phe Gly Glu Ala Asp Ser Gly Ser Arg Cys Cys Leu Lys Ile att ctt ggt ttt tat cta atc aga tat tca ttg att acc tac cag gtg 256 Ile Leu Gly Phe Tyr Leu Ile Arg Tyr Ser Leu Ile Thr Tyr Gln Val 15 20 cgt g 260 Arg

<213> Homo sapiens

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<210> 188
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 <222> 112
 <223> n=a, g, c or t
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                                                          Met Lys
 att ctt tac ctt ttt ttc ttt ttg aaa tgg agt cac cca ggc tgg agt
                                                                       105
 Ile Leu Tyr Leu Phe Phe Phe Leu Lys Trp Ser His Pro Gly Trp Ser
                         -10
gca acg ncg tgg tct tgg cac act gca acc tcc gcc tcc ctg att caa
                                                                       153
Ala Thr Xaa Trp Ser Trp His Thr Ala Thr Ser Ala Ser Leu Ile Gln
                                     10
gtg att ctc ccg cct tgg g
                                                                       172
Val Ile Leu Pro Pro Trp
<210> 189
<211> 150
<212> DNA
<213> Homo sapiens
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<222> 47..148
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tatcacwtct aagagatttc tggtgaaact tgtggatttt ctatac atg aca cca
                                                                        55
                                                    Met Thr Pro
tgt ttt ctg caa atg gac aat ttg act cct ctt ttc cta tct gga tgc
                                                                       103
Cys Phe Leu Gln Met Asp Asn Leu Thr Pro Leu Phe Leu Ser Gly Cys
            -20
                                 -15
ttt tta ttt ctc tct cwt tgc wtg att tat ttg gct agg att ttg gg
                                                                       150
Phe Leu Phe Leu Ser Xaa Cys Xaa Ile Tyr Leu Ala Arg Ile Leu
<210> 190
<211> 339
<212> DNA
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<220>

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 <222> 195..338
<221> sig_peptide
 <222> 195..314
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                                                                        60
agageteetg teeggtgtge cageageeeg gaetggeggt gagegegagg gaggetackg
                                                                       120
agaagcccgg cgacggagga acgcaggtct gctgccaggg attgaggaga ctgaagaacg
                                                                       180.
ctgaagacag gctg atg ggc tca gct ggt agg ctc cac tat ctc gsc atg
                                                                       230
                 Met Gly Ser Ala Gly Arg Leu His Tyr Leu Xaa Met
                 -40
                                     -35
act get gaa aat eee act eet gga gae etg get eeg kee eee etc ate
                                                                       278
Thr Ala Glu Asn Pro Thr Pro Gly Asp Leu Ala Pro Xaa Pro Leu Ile
           -25
                                 -20
act tgc aaa ctc tgc ctg tgt gag cag tct crt gga caa gat gac cac
                                                                       326
Thr Cys Lys Leu Cys Leu Cys Glu Gln Ser Xaa Gly Gln Asp Asp His
                             -5
act cca gga atg c
                                                                       339
Thr Pro Gly Met
5
<210> 191
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<223> Von Heijne matrix
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                                                                       60
aataaatcag gittcattgt tatattattt accac atg aat cac ctt cct cct
                                                                       113
                                       Met Asn His Leu Pro Pro
                                                        -45
aac cat tat agg mgc cat gtg ttc aca tgt cat gtg gac cag tat tta
                                                                       161
Asn His Tyr Arg Xaa His Val Phe Thr Cys His Val Asp Gln Tyr Leu
                                -35
                                                  - 30
act gtg gaa acc gcg ggt ggc atg gag aag gag gca gtg tcc gtg act
                                                                       209
Thr Val Glu Thr Ala Gly Gly Met Glu Lys Glu Ala Val Ser Val Thr
        -25
                            -20
gtg ctg ctc tcc gca gcc ccc tgc ctg ctg tcc tgt ttc ctc ggc tcc
                                                                      257
Val Leu Leu Ser Ala Ala Pro Cys Leu Leu Ser Cys Phe Leu Gly Ser
teg gtg tet gga etg geg tte tgg gtt tee eag eag aaa aet aaa ggg
                                                                      305
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Ser '	Val	Ser	Gly	Leu 10	Ala	Phe	Trp	Val	Ser 15	Gln	Gln	Lys	Thr	Lys 20	Gly	.*
сса	gag	a gg	tgt	aaa	aac	aca	cac	cac	tbg	gca	gnt	aat	aat	ttc	ccc	353
Pro (	Glu	Arg	Cys 25	Lys	Asn	Thr	His	His 30	Хаа	Āla	Xaa	Asn	Asn 35	Phe	Pro	1
gcg a															•	. 359
<210:																
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		q FL	<b>FMLP</b>	LWCS	1GT/	CT	-									•
<400:			acca	aat a	t at	aaac	tcac		+a+=	ato	tasa	taat	++ ~			- 60
gggaa	aaag	ga t	agct	tgag	t cc	agga	gtto	gac	atca	tcc	taga	caac	at a	ggag	gate	a 60 = 120
tgtct	cta	ca a	aacc	ta a	tg a	ac a	aa a	tt a	aa g	jaa a	ac a	ca c	ac a	ca c	ac	170
				-	40	sn L			_	35	•			-	30	
aca c	ac	aca (	cac	aca (	cac	aaa	aac	aac	acc	aaa	cta.	gtg	tca	aac	cta	218
Thr H	ils	ını ı		-25	nis	Lys .	ASN	Asn	-20	гÀг	Leu	vaı	Ser	Asn -15	Leu	
ttc c									tcc					aca	g	264
Phe I	eu		Met 1 -10	Leu 1	Pro	Leu '		Cys -5	Ser	Ile	Gly	Thr	Cys 1	Thr		
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		I LFL		TENV	/LA/I	HP										
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tgtat																
ttcgt																120
tgttt	aaga	aa tg	gaaa	acat	aaa	aata			Asp			ggc	_	Asn		173
ttc a	as s	940 A	ta c	ct a	itt -	nta -	at •	-+-	-40 att 1	rat 4	eta 1	rat -	7 <b>t</b> = -	-35 : 35	a t a	222
Phe A		ys I					sn I					Tyr V				221
cat a	ta c			ta t	tt t	ta t			ctc 1	ttt a	aca o			gta 1	tta	269
His I	le F	lis L	ys L	eu P	he I	eu I	yr 5	Ser 1	Leu 1	Phe 1	Thr (	3lu <i>1</i> -5	lsn '	/al I	Leu	200

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 Ala His Pro Cys Ile Val Leu Arg Arg Leu
     1
 <210> 194
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 <221> CDS
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 <222> 105..203
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                                                                        60
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                                                                       116
                                                   Met Gly Arg Leu
 cat cgt ccc agg agc agc acc agc tac agg aac ctg ccg cat ctg ttt
                                                                       164
 His Arg Pro Arg Ser Ser Thr Ser Tyr Arg Asn Leu Pro His Leu Phe
                 -25
                                     -20
 ctg ttt ttc ctc ttc gtg gga ccc ttc agc tgc ctc ggg agt tac agc
                                                                       212
 Leu Phe Phe Leu Phe Val Gly Pro Phe Ser Cys Leu Gly Ser Tyr Ser
                                 -5 .
 cgg
                                                                       215
Arg
 <210> 195
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<222> 78..158
<223> Von Heijne matrix
      score 7
      seq RLLLLLLXLPLP/PP
<221> misc feature
<222> 73..74
<223> n=a, g, c or t
<400> 195
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                                                                        60
agtetettga tenntae atg caa tee eag gea get ege gaa eac aaa eec
                                                                       110
                   Met Gln Ser Gln Ala Ala Arg Glu His Lys Pro
                                                -20
ggg ghc agc cgc cta ctg ctg ctg ctg ctg cwg ctg ccg ctg cct
                                                                       158
Gly Xaa Ser Arg Leu Leu Leu Leu Leu Leu Xaa Leu Pro Leu Pro
                         -10
ccg ccg gkv ctg cga acc cgg gdy ttt tca wgc acc aca ctc acc gcm
                                                                       206
Pro Pro Xaa Leu Arg Thr Arg Xaa Phe Ser Xaa Thr Thr Leu Thr Ala
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1
                                     10
                                                         15
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999
Gly
<210> 196
<211> 363
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tgagcttgtt ttcctgcaac tagatggtcc caactagacc aggtgatggg agacaatgac
                                                                       120
agatcattag gcattagatt atcataagga gcatacaacc tagatccctt gcatgtgcag
                                                                       180
ttaataatag gttttgcact tctatgagga tctaatgcgg cctctgatct gacaaggggc
                                                                       240
ggastcaggc agtaatggga gcaatgggga gcggttttca atacag atg agg ctt
                                                                       295
                                                    Met Arg Leu
tgg tca ctt gcc tgc ctt tca cct cct gct gtg cag ctt ggt tcc caa
                                                                       343
Trp Ser Leu Ala Cys Leu Ser Pro Pro Ala Val Gln Leu Gly Ser Gln
        -10
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cag gcc acg gac tgg tgg tc
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Gln Ala Thr Asp Trp Trp
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atg tea ect ttg ttt att etg att gtg ett att tgg ate tte tet tte
                                                                      105
Met Ser Pro Leu Phe Ile Leu Ile Val Leu Ile Trp Ile Phe Ser Phe
                    -20
                                        -15
ttt ttc ttt att act cta gtt agg ggg tct atc aat ctt ttt ttt ttt
                                                                      153
Phe Phe Phe Ile Thr Leu Val Arg Gly Ser Ile Asn Leu Phe Phe
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tt
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atg aat ttg ggg gga cat tca gat cat agc act ttt ctt ttc ttt ctt
                                                                      107
Met Asn Leu Gly Gly His Ser Asp His Ser Thr Phe Leu Phe Phe Leu
                            -15
ttt ttt tct gtt ttt tgt ttt ttt t t
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Phe Phe Ser Val Phe Cys Phe Phe Phe
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                                                  Met Leu Asp Phe
gcg atc ttc gcc gtt acc ttc ttg ctg gcg ttg gtg gga gcc gtg ctc
                                                                      105
Ala Ile Phe Ala Val Thr Phe Leu Leu Ala Leu Val Gly Ala Val Leu
                            -10
tac ete tat eeg get tee aga eaa get gea gga att eea ggg att aet
                                                                      153
Tyr Leu Tyr Pro Ala Ser Arg Gln Ala Ala Gly Ile Pro Gly Ile Thr
                                        10
cca act gaa gaa aaa gat ggt aat ctt cca gat att gtg aat agt gga
                                                                      201
Pro Thr Glu Glu Lys Asp Gly Asn Leu Pro Asp Ile Val Asn Ser Gly
                20
                                    25
agt ttg cat gag tbc ctg gtt aat ttg cat gag aga tat ggg cct gtg
                                                                      249
Ser Leu His Glu Xaa Leu Val Asn Leu His Glu Arg Tyr Gly Pro Val
                                40
gtc tcc ttc tgg ttt ggc agg cgc ctc gtg gtt agt ttg ggc act gtt
                                                                      297
Val Ser Phe Trp Phe Gly Arg Arg Leu Val Val Ser Leu Gly Thr Val
        50
gat gta ctg aag cag cat cgg gg
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Asp Val Leu Lys Gln His Arg
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                                            Met Ala His Cys Ser
                                                        -15
tta gaa ctc ttg ggc tca agc agt cct ccc atc tca gcc tcc caa agc '
                                                                       102
Leu Glu Leu Leu Gly Ser Ser Pro Pro Ile Ser Ala Ser Gln Ser
            -10
act gga att aca agc gtg agc ca
                                                                       125
Thr Gly Ile Thr Ser Val Ser
    5
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ctttttattt tttattg atg ccc agc cag ttg ttg ttg tct ctt tct
                                                                      110
                   Met Pro Ser Gln Leu Leu Leu Ser Leu Ser
                           -15
                                               -10
ctc ttt ttg ttt ttt tgg aga cag agt ctc gtt ttg tgg ccc agg ctg
                                                                      158
Leu Phe Leu Phe Phe Trp Arg Gln Ser Leu Val Leu Trp Pro Arg Leu
gag tgc agt tgt gtc att gcg gct cac tgc agc ctg acc tcc cag gct
                                                                      206
Glu Cys Ser Cys Val Ile Ala Ala His Cys Ser Leu Thr Ser Gln Ala
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cgg g
                                                                      210
Arg
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437

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cgc Arg		30	35	440
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	s Lys Val Phe Thr		cct acc aaa cat att Pro Thr Lys His Ile -20	224
		Val Ser Phe	ctc ttg ctg ctt tta Leu Leu Leu Leu Leu	272
gga tcc cgg gg Gly Ser Arg 1				283
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tca tcc gtc cac Ser Ser Val His	ctc ctt gtc ttc Leu Leu Val Phe -20	aag gac cac Lys Asp His -15	ctc ctc tcc atg ctg Leu Leu Ser Met Leu -10	166
	ggg gcc tgc tgc	cca tct aca	cct cac gag ggc act Pro His Glu Gly Thr	214
agg agc acg gtt	tcc tgg atc cca	cca aca tac	aaa gca qcc aca caq	262

_	Ser 10	Thr	Val	Ser	r Trp	Ile 15	Pro	Pro	Thr	Tyr	Lys 20		Ala	Thr	Gln	264
gg <210	1 - 2	.08							•							264
<213 <212																•
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	_			4.												
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		core					6									
	S	eq L	LSMF	CVSH	TVQT	(/ A1										
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_	_	_										_	_	-	igtgct	
															catato	300
tttt	ttc	ttc 1	tctc	cgtg	ta g	ttcta	aaaa	a tga	acca	tatg	ata	ttcct	tg a	a ato	ggta	357
															: Val	,
_		tct Ser				_	_		. –						-	405
_		-15		,			-10					-5			•	
aca	gca	aca	tac	aca	ca				•							422
Thr	Ala	Thr	Tyr	Thr												
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~223		core	_			73486										
	_	ea AL					,									
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									_			- 1				
		ttt										cca	cgt			104
	Ser	ttt Phe				Ala					Ala	cca	cgt		Tyr	104
Ser	Ser -10		Thr	Trp	Trp	Ala -5	Pro	Ala	Cys	Cys	Ala 1	cca Pro	cgt Arg	Thr	Tyr 5	104 152

				10					1 =					20			
cag Gln	agt Ser	aga Arg	aca Thr 25	tcg	acc Thr	aaa Lys	gga Gly	aag Lys	15 ; tta ; Leu	tgg Trp	ccg Pro	ttt Phe	999 Gly	20 g		•	195
<21 <21	0 > 2 1 > 3 2 > D 3 > H	63	sapio	ens			-										
	1> C	DS	361														
<22	2 > 2 3 > V s	ig_pe 12 on He core eq Ki	280 ≥ijne 6.80	e mai	0190		6										•
taai atga aati	aagt toot	cat o	ttca gtcac	tgt	gc to ga ct	gctg1 :gctd	tcaa catc	g tc a gc a t	atcc aggc atg	attg aagg	ata aag ttc Phe	ctgt agca aca	ttt ggc ttc	gcgg aaca cag		ı	60 120 180 232
att Ile	999 Gly -15	gga Gly	aaa Lys	ctg Leu	cta Leu	tta Leu -10	tct Ser	ggt Gly	tta Leu	aca Thr	cag	gag	tgc Cys	ctt Leu	ggt Gly	-	280
gcc Ala 1	ctg	cct Pro	gag Glu	gct Ala 5	aat Asn	gtg	ttc Phe	tgt Cys	agg Arg 10	ggt Gly	ggc	tgc Cys	aca Thr	Ala	aca Thr		328
gtc		aaa Lys		999					gag		ag			15		÷	363
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Val	Arg		Ala <i>i</i> -25	Asn	Ile .	Arg	Met	Gln -20	Cys	Lys	Ilė	Tyr	Asp -15	Ser	Leu		286
ctg	gct	ctt	tct (	ccg	gac	cta	cag	gca	gcc	aga	ggr	ctg	atg	tgt	gct		334

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Leu Ala Leu Ser Pro Asp Leu Gln Ala Ala Arg Gly Leu Met Cys Ala
                              - 5
 gct tcc gtg atg tcc ttc ttg gct ttc atg atg g
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Ala Ser Val Met Ser Phe Leu Ala Phe Met Met
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                                                                       120
gggccgtatg gcatttgggc aatattgatt cttcctattc atgagcatgg aatgtttttc
                                                                       180
cattigitica igiccicict tattitigitig agcagiggit igitagiticic citigaagggg
                                                                       240
ttcttcacat cccttgtaag ttgtattccc aggtatttta ttctctttgt agcaattttg
                                                                       300
aatgggagtt cacte atg att tgg ete tet ttt tgt eta tta ttg gtg tat
                                                                       351
                  Met Ile Trp Leu Ser Phe Cys Leu Leu Leu Val Tyr
                  -40
agg aat get tgt gat ttt tge aca ttg act tta tat eet ggg act ttg
                                                                       399
Arg Asn Ala Cys Asp Phe Cys Thr Leu Thr Leu Tyr Pro Gly Thr Leu
             -25
                                 -20
                                                    -15
ctg aag ttg ctt atc agc tta agg agt ttt tgg gct gag acg acg ggg g
Leu Lys Leu Leu Ile Ser Leu Arg Ser Phe Trp Ala Glu Thr Thr Gly
                             -5
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      seg LVGSLHLFLSVLA/SK
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                                                                        54
                              Met Phe Ser Ser Pro Gly Leu Arg Thr
                              -25
                                                   -20
ctc ttt gta ttg gta ggc agc ctg cac ttg ttc ctt tca gtc ctg gca
                                                                       102
Leu Phe Val Leu Val Gly Ser Leu His Leu Phe Leu Ser Val Leu Ala
    -15
                        -10
agt aaa agc agg aat tot aaa aag caa cga tta tto oto ota gtt oot
                                                                       150
Ser Lys Ser Arg Asn Ser Lys Lys Gln Arg Leu Phe Leu Leu Val Pro
                                    10
ttg tac ag
                                                                      158
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      seg NVCSLPAPGLCSG/QP
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                                                                       56
                                          Met Leu Thr Asp Gly Ile
                                                       -20
cta atg aga gtc aat gtg tgc tca ctg cca gct cct ggg ctg tgc tct
                                                                      104
Leu Met Arg Val Asn Val Cys Ser Leu Pro Ala Pro Gly Leu Cys Ser
        -15
                            -10
ggt cag cca ggt gtg agg gcc tgg cct ggg gtc aca cag ctg act car
                                                                      152
Gly Gln Pro Gly Val Arg Ala Trp Pro Gly Val Thr Gln Leu Thr Gln
                                        10
bta gag gaa tgc cca tgg ttc tca gca ttg gaa gga ctg gg
                                                                      193
Xaa Glu Glu Cys Pro Trp Phe Ser Ala Leu Glu Gly Leu
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                                                                       60
caaagc atg ttt aac tgg aac cca tgg cta act act tta atc act ggg
                                                                      108
      Met Phe Asn Trp Asn Pro Trp Leu Thr Thr Leu Ile Thr Gly
                   -30
                                       -25
wta gch gga cct ctc ctc atc cta cta tta agt tta att ttt ggg cct
                                                                      156
Xaa Ala Gly Pro Leu Leu Ile Leu Leu Ser Leu Ile Phe Gly Pro
                -15
                                    -10
                                                        - 5
tgt ata tta aat tcg ttt ctk aat tkt ata aaa caa cgc ata gct tct
                                                                      204
Cys Ile Leu Asn Ser Phe Leu Asn Xaa Ile Lys Gln Arg Ile Ala Ser
ggc aaa cgg g
                                                                      214
Gly Lys Arg
    15
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                                                                     51
                        Met Ala Gly Ser Arg Gln Arg Gly Leu Arg
                                       -25
99
Ala Arg Val Arg Pro Leu Phe Cys Ala Leu Leu Leu Ser Leu Xaa Xaa
               .-15
                                   -10
                                                       -5
mty ckt ccg rkg cka cgs cgt gkg agg aga ccc cgc ggt cgc gtt gcc
                                                                    147
Xaa Xaa Pro Xaa Xaa Arg Arg Xaa Arg Arg Pro Arg Gly Arg Val Ala
aca tcg ccg ttt cga gta saa ata cag ctt caa ggg gcc gca cct ggt
                                                                    195
Thr Ser Pro Phe Arg Val Xaa Ile Gln Leu Gln Gly Ala Ala Pro Gly
                       20
gca gag cga cgg gac cgt gcc ctt ctg ggm cca cgc ggg gaa tgc tat
                                                                    243
Ala Glu Arg Arg Asp Arg Ala Leu Leu Gly Pro Arg Gly Glu Cys Tyr
                   35
                                       40
tcc aag ttc aga tca aat tcg agt agc acc atc ttt aaa aag cya aag
                                                                    291
Ser Lys Phe Arg Ser Asn Ser Ser Ser Thr Ile Phe Lys Lys Xaa Lys
                50
                                   55
agg ctc agt gtg gvm aam gac aav agc gga cct ggg
                                                                    327
Arg Leu Ser Val Xaa Xaa Asp Xaa Ser Gly Pro Gly
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gaactcacc atg gag ttt ggg ctg agc tgg gtt ttc ctt gtt gct att tta
                                                                    111
         Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Leu
                         -15
                                             -10
aaa ggt gtc cac tgt gac gtg cag ctg gtg gag tcc ggg gga ggt tta
                                                                    159
Lys Gly Val His Cys Asp Val Gln Leu Val Glu Ser Gly Gly Leu
-5
gtt cag cct ggg ggg tcc ctg aga ctc tcc tgt gca gcc tct gga ctc
                                                                   207
Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Leu
                               20
acc ctc agt aac gac tgg atg cac tgg gtc cgc caa gcc cca ggg aag
                                                                   255
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Thr Leu Ser Asn Asp Trp Met His Trp Val Arg Gln Ala Pro Gly Lys
ggg ctg gtg tgg gtc tca cac att gat agt tct rgg act atc aca aat
                                                                        303
Gly Leu Val Trp Val Ser His Ile Asp Ser Ser Xaa Thr Ile Thr Asn
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tac gcg gac tcc gtg aag ggc cga ttc acc atc tcc aga gac aac gcc
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Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
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                                                                       109
               Met Gly Leu Phe Leu Gly Phe Leu Ala Cys Ser Val
               -15
gca tac cag tgc cat tct gct ttt gtt act gta gct tca cag tac act
                                                                       157
Ala Tyr Gln Cys His Ser Ala Phe Val Thr Val Ala Ser Gln Tyr Thr
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Leu Lys Ser Glu Thr Leu Met Pro Ala Ala
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                                                                      -103
Arg Asn Lys Arg Gly Gly Arg Trp Leu Val Ser Leu Ala Lys Gln Gln
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cgc cac att gag ctg gac cgg ctg tgg ctg gag acg ttc tcc gtg ttc
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Arg His Ile Glu Leu Asp Arg Leu Trp Leu Glu Thr Phe Ser Val Phe
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WO 99/53051 PCT/IB99/00712 127 ctc ggt ctc atc ttc ttc ctg gag ctg gca aca ggg atc ctg gcc ttt Leu Gly Leu Ile Phe Phe Leu Glu Leu Ala Thr Gly Ile Leu Ala Phe -10 - 5 gtc ttc aag gac tgg att cga gac cag ctc aac ctc ttc atc aac aac 247 Val Phe Lys Asp Trp Ile Arg Asp Gln Leu Asn Leu Phe Ile Asn Asn 10 15 aac gtc aag gcc tac cgg gac gac att gac ctc cag arc ctc att gac 295 Asn Val Lys Ala Tyr Arg Asp Asp Ile Asp Leu Gln Xaa Leu Ile Asp 25 30 ttt gct cag gaa tac tgg tct tgc tgc gga scc gag gcc cca ata rdt 343 Phe Ala Gln Glu Tyr Trp Ser Cys Cys Gly Xaa Glu Ala Pro Ile Xaa 40 gga acc ggg g 353 Gly Thr Gly 55 <210> 220 <211> 115 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 12..113 <221> sig\_peptide <222> 12..53 <223> Von Heijne matrix score 6.59999990463257 seg FLSLSTAFWVVYA/MI <400> 220 actageattt c atg ttt tta tet etc tet act gea tte tgg gta gtt tat 50 Met Phe Leu Ser Leu Ser Thr Ala Phe Trp Val Val Tyr -10 gcc atg ata att tat tca gct ctc tct gct gga ttt att att ttc ttt 98 Ala Met Ile Ile Tyr Ser Ala Leu Ser Ala Gly Phe Ile Ile Phe Phe 10 tta gtt gtg ttt aat ct 115 Leu Val Val Phe Asn <210> 221 <211> 142 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 29..142 <221> sig\_peptide <222> 29..130 <223> Von Heijne matrix score 6.59999990463257 seq FFLFFCFETGSHS/VT <400> 221 cctgcccatt gcttcaacct gcacctct atg tac att gtg atg gat cta cct 52 Met Tyr Ile Val Met Asp Leu Pro

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Leu Trp Leu Ser His Glu Val Gln Ser Tyr Ile Pro Ser Phe Phe Leu

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-25
                        -20
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tgccacagct tagttagctt tgagagggaa agggtagaat ccatttaagg agacaggtta
                                                                    180
aaaaatgata tatttaagca tataggca atg gta gca cat gat tac caa aac
                                                                    232
                              Met Val Ala His Asp Tyr Gln Asn
                                      ~25
ata att agc ctt ttc ttt ctt gct ttt tca ttt tct ttc ttt cct tct
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Ile Ile Ser Leu Phe Phe Leu Ala Phe Ser Phe Ser Phe Phe Pro Ser
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                                   -10
328
Ser Phe Ser Ser Phe Phe Leu Xaa Phe Leu Ser Phe Phe Ser Ser Phe
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                       Met Ala Ala Leu Arg Ala Leu Cys Gly Phe
                       -15
                                           -10
cgg ggc gtc gcg gcc cag gtg ctg cgg mct ggg gct gga gtc cga ttg
                                                                    99
Arg Gly Val Ala Ala Gln Val Leu Arg Xaa Gly Ala Gly Val Arg Leu
ccg att cag ccc agc aga ggt gtt cgg cag tgg cag cca gat gtg gaa
                                                                   147
Pro Ile Gln Pro Ser Arg Gly Val Arg Gln Trp Gln Pro Asp Val Glu
tgg gca cag cag ttt ggg gga gct gtt atg tac cca agc aaa gaa aca
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Trp Ala Gln Gln Phe Gly Gly Ala Val Met Tyr Pro Ser Lys Glu Thr gcc cac tgg aag cct cca cct tgg aat gat gtg gac cct cca aag gac 243 Ala His Trp Lys Pro Pro Pro Trp Asn Asp Val Asp Pro Pro Lys Asp aca att gtg aag aac att acc ctg aac ttt ggg ccc caa cac cca gca 291 Thr Ile Val Lys Asn Ile Thr Leu Asn Phe Gly Pro Gln His Pro Ala 65 70 gcg cat ggt gtc ctg cga cta gtg atg gaa ttg agt ggg gag atg gtg 339 Ala His Gly Val Leu Arg Leu Val Met Glu Leu Ser Gly Glu Met Val cgg aag tgt gat cct cac atc ggg ctc ctg cac cga ggc act gag aag 387 Arg Lys Cys Asp Pro His Ile Gly Leu Leu His Arg Gly Thr Glu Lys 100 ctc att gaa tac aag rcc tat ctt cag gcc ctt cca tac ttt ga 431 Leu Ile Glu Tyr Lys Xaa Tyr Leu Gln Ala Leu Pro Tyr Phe 110 115 <210> 224 <211> 282 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 132..281 <221> sig\_peptide . <222> 132..215 <223> Von Heijne matrix score 6.5 seq LVFLHLFLXVYLG/LV <400> 224 attttaaagt gtttctgtta atgtattcta cttcagtccc ccaaaattcc aactaacgac 60 atacatgaat aacagatcat gactgctgtt tctacaagcc tttctgctca ctgtgcttcc 120 acttacaact c atg tta ata tgg tot tcc tct tct ttt cct gca ccc cct 170 Met Leu Ile Trp Ser Ser Ser Ser Phe Pro Ala Pro Pro -25 ctc ttt ctt gtc ttt ctt cat ctt ttc ctt mwt gtc tat ttg ggt ctt 218 Leu Phe Leu Val Phe Leu His Leu Phe Leu Xaa Val Tyr Leu Gly Leu -10 - 5 gtc atg ccc act caa cag tat ctc ctc ctg cag agt cca ttg atg ttc 266 Val Met Pro Thr Gln Gln Tyr Leu Leu Gln Ser Pro Leu Met Phe aca gac aaa gcc cag c 282 Thr Asp Lys Ala Gln <210> 225 <211> 198 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 26..196 <221> sig\_peptide <222> 26..163 <223> Von Heijne matrix score 6.5

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Trp Ile Asn Val Cys His Gly Asp Leu Leu His Arg Ser Ser Arg Arg -35 -30 -25	. 100
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Leu Gly Val Lys Pro Ser Thr His Trp Leu Phe Phe Leu Met Leu Ser -20 -15 -10	148
ctt tgc acc cct cct gac aga ccc tgg tgt gtg ttg ttc ccc ccg ctg Leu Cys Thr Pro Pro Asp Arg Pro Trp Cys Val Leu Phe Pro Pro Leu	196
-5 1 5 10 gg	
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c400> 226 gcagttgakr dsacttggta atg tsa acg caa gaa gca ggc ttg aty ttt ttt  Met Xaa Thr Gln Glu Ala Gly Leu Ile Phe Phe  -30 -25'  tct ccc ccc ttc tct ctc tct ctc tct ctc ctc ctc ctc Ser Pro Pro Phe Ser Leu Ser Leu Ser Leu Ser Leu Pro Leu Ser Leu  -15 -10 -5  tyt ctc ctc tst sac cca cac tca cgc aca cct caa agg g  Kaa Leu Leu Xaa Xaa Pro His Ser Arg Thr Pro Gln Arg  1 5  (2210> 227  (2211> 206  (2212> DNA  (2213> Homo sapiens  (2222> 77205  (2222> 77115  (2223> Von Heijne matrix  score 6.5	101
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                                        Met Met Val Thr Tyr Arg.
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                                                                       281
Trp Gly Phe Gly Val Asp Val Xaa Phe Val Ala Val Asp Ala Ile Pro
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                        -25
                                             -20
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                                                                      329
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                                        -5
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Ser Val Gly Val Cys Trp Arg Ser Thr Pro Asp Pro Val Cys Leu Gly
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atc acc agc aga ggc tgc aga aca gaa ata ttg cag aac agc aaa tgt
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Ile Thr Ser Arg Gly Cys Arg Thr Glu Ile Leu Gln Asn Ser Lys Cys
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                           . 25
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                                                                        102
 Leu Pro Glu Ile Phe Leu Pro Phe Ser Leu Ser Pro Ala Asn Ala Gln
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                      -10
                                          - 5
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                                                                       397
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                    -10
                                         -5
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Leu Thr Ser Ser
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96

144

301

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134
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gcg atg ctc ctc act ttc agc tcc agc tcc cgc cac cgc ctc tat
   Met Leu Leu Thr Phe Ser Ser Ser Arg His Arg Arg Leu Tyr
                   -30
                                      -25
cgc cgc cgc cgc cac cac ctc ctc ttc gtt gtc ctc ctt cct ccg
Arg Arg Arg His His Leu Leu Phe Val Val Leu Leu Pro Pro
               -15
                                   -10
cct ggc agc gtt gkt ctc tgc agc sgg nrm grn smv raa gtg ctr vbg
Pro Gly Ser Val Xaa Leu Cys Ser Xaa Xaa Xaa Xaa Xaa Val Leu Xaa
                          5 -
```

kma sga aag ttc cgg gan gga cta cat gga gcc atg ctc cct ggg ctc 192 Xaa Xaa Lys Phe Arg Xaa Gly Leu His Gly Ala Met Leu Pro Gly Leu 20 ttc cgc ggg cgc ccg cgc gct gcc ctt cgc ttg aga gtc tca ccg wgt 240 Phe Arg Gly Arg Pro Arg Ala Ala Leu Arg Leu Arg Val Ser Pro Xaa 35 40 tgc cca ggc tgg aaa gtg gcg cga tct cgg ctc aca gca acc tcc gcc 288 Cys Pro Gly Trp Lys Val Ala Arg Ser Arg Leu Thr Ala Thr Ser Ala 50

55

-10

tcm cgg gmc cgg g Ser Arg Xaa Arg

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<213> Homo sapiens

<220>

<221> CDS

<222> 152..247

<221> sig\_peptide

<222> 152..190

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ageggtgtga ggtgcttggt ageggeget agetgettee aegteettge tteaceteag	120
gtaaagagag aagtaatgga aggcctgtct g atg ttg ctt ctt ttg caa cta Met Leu Leu Leu Gln Leu	172
-10	
aac tta aaa aca ctc tca tcc agt acc ata gca ttg aag aag ata agt Asn Leu Lys Thr Leu Ser Ser Ser Thr Ile Ala Leu Lys Lys Ile Ser	220

ggc gag ttg cta aga aaa cga aag agg g Gly Glu Leu Leu Arg Lys Arg Lys Arg

248

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       seq LFVLLIITQLLYG/GI
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                                                                        60
 agatttgaac aacatggtaa tcatgtgatg gacatggaaa agtgractaa cbtkrgggat
                                                                       120
 cwtggtargg tcaytaagaa taactckaat cawgatgtta aaaggctttc ctttacattc
                                                                       180
 acaaaacaat ttrstteeta gaagtagttt attettgeet gtggteattt ttgeteettt
                                                                       240
 ataatactac atctaaatca atttgttaaa tatagtagag aaatgaaata aatttcttcc
                                                                       300
agttaaacca ctgcacttaa agagtagaaa ccctctct atg tca ctc ttt gtt ttg
                                                                       356
                                           Met Ser Leu Phe Val Leu
                                            -15
ttg atc ata act caa ctg ctg tat ggt ggg ata ctc t
                                                                       393
Leu Ile Ile Thr Gln Leu Leu Tyr Gly Gly Ile Leu
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<223> Von Heijne matrix
      score 6.40000009536743
      seq ILFLGVLLSASDL/CV
<400> 236
ttttgagtta atttttgtat aagttgtaag gattaggtca gggttcttaa gaaaaatatt
                                                                       60
gttttggtct atagatgtct cattgcttct gtgctatttg ttggaaaagc tgttcttcca
                                                                      120
atg aat tgc ttt tgc aat ttt gtc aaa acc agt gag gca tat atg att
                                                                      168
Met Asn Cys Phe Cys Asn Phe Val Lys Thr Ser Glu Ala Tyr Met Ile
                                -20
ctg ttt cta ggt gtt cta ctc tct gca agt gat tta tgt gtc tat ccc
                                                                      216
Leu Phe Leu Gly Val Leu Leu Ser Ala Ser Asp Leu Cys Val Tyr Pro
        -10
                            -5
atc ggg
                                                                      222
Ile Gly
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<211> 154
<212> DNA
<213> Homo sapiens
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<220>

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       seg SVILALWEAEAGG/SP
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 agtettttge teetgtggtt aagattatte tgetaggetg etcaeggtgg etg atg
                                                                         56
 tet gta ate eta gea ett tgg gag gee gag geg gge teg eet gag
                                                                        104
 Ser Val Ile Leu Ala Leu Trp Glu Ala Glu Ala Gly Gly Ser Pro Glu
              -10
                                  -5
 atc ggg agt tcg gga ccg gcc gca cca aca tgg aga agc ccc gtc cag
                                                                       152
 Ile Gly Ser Ser Gly Pro Ala Ala Pro Thr Trp Arg Ser Pro Val Gln
                         10
                                              15
 99
                                                                       154
 <210> 238
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 <212> DNA
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       score 6.30000019073486
      seq LGCLLLAVRSSAT/VN
<221> misc_feature
<222> 359..360,381
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tcaccacaat caattttaga acattttcat catcccgaaa ataagccctg ttccctttag
                                                                        60
ctgtcactcc ccactcctac cccccagccc tgtgcaataa tctactttct gtctttgaag
                                                                       120
ctttgcctat tctggacatt ttgtataaaa gggtttgtgg aggatgtggt cttttgtgac
                                                                       180
tggcttcttg aacttggcat agtgttttca aggttcaacc atgttgtagc acgtacgttc
                                                                       240
ctttttatgg ccaa atg tac gga gag tcc aca ttg ttt atc cat tca tca
                                                                       290
                Met Tyr Gly Glu Ser Thr Leu Phe Ile His Ser Ser
                                 -25
gtt cat ggg cat ttg ggt tgt ctc ctc ttg gct gtt agg agt agt gct
                                                                       338
Val His Gly His Leu Gly Cys Leu Leu Leu Ala Val Arg Ser Ser Ala
        -15
act gtg aac att acg tac chn nkw gtk tgt gtg gac att cak ntt cat
                                                                       386
Thr Val Asn Ile Thr Tyr Xaa Xaa Val Cys Val Asp Ile Xaa Xaa His
                    5
ttc cat atg ctt atg tct gga att act ggg tca tat ggc aac tct ctt
                                                                      434
Phe His Met Leu Met Ser Gly Ile Thr Gly Ser Tyr Gly Asn Ser Leu
                20
tca ct
                                                                      439
Ser
<210> 239
<211> 229
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137	
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<222> 7228	
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atg cta tct ctc ttc cga ggt tct cac aga gtt cag gt Met Leu Ser Leu Phe Arg Gly Ser His Arg Val Gln Va -35 -30 -2	l Thr Leu Arg
aag aca ttt tgc aca acc tca agt tgg tta tac ctt ct Lys Thr Phe Cys Thr Thr Ser Ser Trp Leu Tyr Leu Le $-20$ $-15$ $-10$	u Glu Val Val
gct cca ctg tca gga atc cac gag tgg aga cct tcc ca Ala Pro Leu Ser Gly Ile His Glu Trp Arg Pro Ser His -5 5	c gtg tgt ctt 192 s Val Cys Leu 10
agc tgt cta ggc agt act tcc tgc aac ccc cct gag g Ser Cys Leu Gly Ser Thr Ser Cys Asn Pro Pro Glu 15 20	229
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ctetteggtt gtecageeet teteceagee etggteeete agaagga ceag atg tta egg tee gee tge gte tet eag eae gee gg	t ggc att tgg 109
Met Leu Arg Ser Ala Cys Val Ser Gln His Ala Gl -65 -60 -55	
gtt gac cgc gga ggc ccc cag tgc cag agg gtg ttc acg Val Asp Arg Gly Gly Pro Gln Cys Gln Arg Val Phe Thr -50 -45 -40	ttc tgc cgt 157 Phe Cys Arg -35
ggg ctc agc cca aac ttt gga cgc tca gag acc caa cgg Gly Leu Ser Pro Asn Phe Gly Arg Ser Glu Thr Gln Arg -30 -25	gag cgc tgg 205
ata agg cca gga cag ctg atg gtt gtg gca gaa aca tct [le Arg Pro Gly Gln Leu Met Val Val Ala Glu Thr Ser -15 -10	Caa ggt agc 253

PCT/IB99/00712

WO 99/53051 138 tgg ten gee eec act tee eea tst ace tet tgt eet eec eec aac ace Trp Ser Ala Pro Thr Ser Pro Xaa Thr Ser Cys Pro Pro Pro Asn Thr asc acc aca ccg gyt cc 318 Xaa Thr Thr Pro Xaa <210> 241 <211> 405 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 123..404 <221> sig\_peptide <222> 123...257 <223> Von Heijne matrix score 6.30000019073486 seg GFVSLLVVHAADA/WV <400> 241 tagctggacc cgtctgggag gtaggtttgt gagcgtgaga gaksgatctg taccgcgggg atccgaagta tgcttatcca ggtgggctgc ctcaagcctc gatcccaccc ccgcgctdvt 120 ag atg gtg tca agg tcc ttg cgt ggg aga agg act tgg gtg aga tgc 167 Met Val Ser Arg Ser Leu Arg Gly Arg Arg Thr Trp Val Arg Cys -40 atg cgg aga ttg ccc cca att ccg gcc tgg agc caa ggg aaa ggg atg 215 Met Arg Arg Leu Pro Pro Ile Pro Ala Trp Ser Gln Gly Lys Gly Met -30 -25 -20 eet gga tit gig tet eta tig gig gie eac get geg gat gee igg gia 263 Pro Gly Phe Val Ser Leu Leu Val Val His Ala Ala Asp Ala Trp Val -10 -5 gcc cag agg ttr tct acg cca tac ttc tca ctg ttt ttg agc ata cct 311 Ala Gln Arg Leu Ser Thr Pro Tyr Phe Ser Leu Phe Leu Ser Ile Pro 10 15 aga tgt tcc ttt cct agg cgg agt ata gat cgc acg tgt tct agc stc 359 Arg Cys Ser Phe Pro Arg Arg Ser Ile Asp Arg Thr Cys Ser Ser Xaa 25 tta gac tca gag ggt tcg agc tct ata asc ccc tcc act ccc ttc a 405 Leu Asp Ser Glu Gly Ser Ser Ser Ile Xaa Pro Ser Thr Pro Phe 35 <210> 242 <211> 242 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 129..242 <221> sig\_peptide <222> 129..191 <223> Von Heijne matrix score 6.30000019073486 seq SLLPCSLISDCCA/SN <400> 242 cttttgtttt gcaatgccct gcccccagag gtggagtcta cagaggcagg caggcctcct

tgagctgagg tgggctccac ccagttcgag cttcccagct gctttgttta cctactcaag

cctgggca atg gtg ggc gcc ctt ccc cca gcc tcg ctt ctg cct tgc agt

60

Met Val Gly Ala Leu Pro Pro Ala Ser Leu Leu Pro Cys Ser -20 -15 -10	•
ttg atc tca gac tgc tgt gct agc aat gag cga ggc tcc atg ggc gta Leu Ile Ser Asp Cys Cys Ala Ser Asn Glu Arg Gly Ser Met Gly Val -5 1 5	218
gga ccc tct gag cca cgg cgy ggg Gly Pro Ser Glu Pro Arg Arg Gly 10 15	242
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seq LGSLIASLAPSTG/LG	
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-20 -15 -10 -5 cca tcg aca ggt ctt ggg	363
Pro Ser Thr Gly Leu Gly	
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x221> sig_peptide x222> 153236 x223> Von Heijne matrix score 6.30000019073486 seq FFLFLFFXEXXXX/XX	
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gtatgtgtg ttaatcotct tgtttaaatg cc atg aaa ctt cag ttt gcc ttt  Met Lys Leu Gln Phe Ala Phe -25	120 173
gt tat ttt ctt tat tta gat acc ttt ttt ctt ttt ctt ttt ttk Lys Tyr Phe Leu Tyr Leu Asp Thr Phe Phe Leu Phe Leu Phe Phe Xaa -20 -15 -10	221
ag ama gyc tkg cyc kgt kgc hta ggm agg agt gca gtg gca maa cct lu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Arg Ser Ala Val Ala Xaa Pro	269

-5	140	
cag ctc ayt gea gcc tcc acc ttc kgg tty cas gea att tty ctg ccc GIN Leu Xaa Ala Ala Ser Thr Phe Xaa Phe GIn Ala Ile Phe Leu Pro 15 20 25 324  cag ckg g GIn Xaa 2 25 324  c2lo 245  c2llo 245  c2llo 246  c2llo DNA  c2llo Sig Deptide  c2co cag gag ctg peptide  c2co cag cfilkVLLFSVVSG/LE  c400> 245  gttgeggggc ggggccttcg cagagc atg gcg gcg gag ctt gag ggt ggc Met Ala Ala Gly Glu Leu Glu Gly Gly -65  aaa ccc ctg agc ggg ctg ctg aat gcg ctg gcc cag gac act ttc cac Lys Pro Leu Ser Gly Leu Leu Asn Ala Leu Ala Gln Asp Thr Phe His -60  c10	10	
Cang ckg g Call xaa  C210	cag ctc ayt gca gcc tcc acc ttc kgg ttv caa gca att ttv gtg acc	22.5
Cag ckg g Gln Xaa  (210: 245 (211: 280 (212: DNA (213: Homo sapiens  (220: 221) CDS (222: 27278  (221) sig_peptide (222: 27233 (223: Von Heijne matrix score 6.30000019073486 seq GILKVLLFSVVSG/LE  (400: 245 gttspcggggc ggggcttcg cagagc atg gcg gcg ggc gag ctt gag ggt ggc Met Ala Ala Gln Apn Thr Phe His -60 -60 -55 -60 -60 -65 ggg tac ccc gag cac aca gag gag ctt ac ag gac act ttc cac Lys Pro Leu Ser Gly Leu Leu Aen Ala Leu Ala Gln Apn Thr Phe His -60 -10 -10 -35 ggg tac ccc gag atc aca gag gag ctt cac gga agc cac tat ac cac Gly Tyr Pro Gly Ile Thr Glu Glu Leu Leu Arg Ser Gln Leu Tyr Pro -40 gag gtg cca ccc gag gag ttc cac ccc ttt ctg cac aga aga gag gag Glu Val Pro Pro Glu Glu Phe His Pro Phe Leu Ala Lys Met Arg Gly -25 att ctt aag gta ctg ctt tt tct gta gtc tcc ggs ttg gag cag aca 11e Leu Lys Val Leu Leu Phe Ser Val Val Ser Gly Leu Glu Gln Apn -10 -5 11e Leu Lys Val Leu Leu Phe Ser Val Val Ser Gly Leu Glu Gln Apn -10 -5 10 -5 11 -10 -10 -5 12 -22 -22 -22 -22 -22 -22 -22 -22 -22	Gln Leu Xaa Ala Ala Ser Thr phe Xaa Dhe Gln Ala Tlo Dhe Leu	, 31/
Cag ckg g   Gln Xaa		
Cln Xaa   Cln		
<pre>&lt;210&gt; 245 &lt;211&gt; 280 &lt;212&gt; DNA &lt;213+ Momo sapiens  </pre> <pre>&lt;220&gt; &lt;221&gt; CDS &lt;221&gt; CDS &lt;221&gt; CDS &lt;221&gt; CDS &lt;222&gt; 27278  </pre> <pre>&lt;221&gt; sig_peptide &lt;222&gt; 27233 </pre> <pre>&lt;222&gt; 27233 </pre> <pre>&lt;223&gt; Von Heijne matrix</pre>		324
<pre></pre>	GII Add	
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<pre></pre>		
<pre>&lt;400&gt; 245 gttgcggggc ggggccttcg cagagc atg gcg gcg ggc gag ctt gag ggt ggc</pre>		
### String of String St	seq GILKVLLFSVVSG/LE	
### String of String St		
### Ala Ala Gly Glu Leu Glu Gly Gly  -65  aaa ccc ctg agc ggg ctg ctg aat gcg ctg gcc cag gac act ttc cac Lys Pro Leu Ser Gly Leu Leu Asn Ala Leu Ala Gln Asp Thr Phe His -60 -55 ggg tac ccc ggc atc aca gag gag ctg cta cgg agc cag cta tat cca Gly Tyr Pro Gly Ile Thr Glu Glu Leu Leu Arg Ser Gln Leu Tyr Pro -40 gag gtg cca ccc gag gag ttc cac ccc ttt ctg gca aag atg agg ggg ggg Glu Val Pro Pro Glu Glu Phe His Pro Phe Leu Ala Lys Met Arg Gly -25 att ctt aag gta ctg ctc ttt tt gta gtc tcc ggc ttg gag cag aca act Ile Leu Lys Val Leu Leu Phe Ser Val Val Ser Gly Leu Glu Gln Asn -10 ccc ttg gcc gct ggc ttc aga ctc tcc cac ccg gg Pro Leu Ala Ala Gly Phe Arg Leu Ser His Pro 5 10  220 221> 211 2212> DNA 2213> Homo sapiens  220> 2213	<400> 245	
### Ala Ala Gly Glu Leu Glu Gly Gly  -65  aaa ccc ctg agc ggg ctg ctg aat gcg ctg gcc cag gac act ttc cac Lys Pro Leu Ser Gly Leu Leu Asn Ala Leu Ala Gln Asp Thr Phe His -60 -55 ggg tac ccc ggc atc aca gag gag ctg cta cgg agc cag cta tat cca Gly Tyr Pro Gly Ile Thr Glu Glu Leu Leu Arg Ser Gln Leu Tyr Pro -40 gag gtg cca ccc gag gag ttc cac ccc ttt ctg gca aag atg agg ggg ggg Glu Val Pro Pro Glu Glu Phe His Pro Phe Leu Ala Lys Met Arg Gly -25 att ctt aag gta ctg ctc ttt tt gta gtc tcc ggc ttg gag cag aca act Ile Leu Lys Val Leu Leu Phe Ser Val Val Ser Gly Leu Glu Gln Asn -10 ccc ttg gcc gct ggc ttc aga ctc tcc cac ccg gg Pro Leu Ala Ala Gly Phe Arg Leu Ser His Pro 5 10  220 221> 211 2212> DNA 2213> Homo sapiens  220> 2213	gttgcggggc ggggccttcg cagagc atg gcg gcg gcg	
aaa ccc ctg agc ggg ctg ctg aat gcg ctg gcc gcc gcc gcc gcc cacc ctg agc ggg ctg ctg aat gcg ctg gcc gcc gcc gcc act ttc cac lol Lys Pro Leu Ser Gly Leu Leu Asn Ala Leu Ala Gln Asp Thr Phe His -50 -45 ggg tac ccc ggc atc aca gag gag ctg cta cac ggg agc cag cta tat caca lagging ctg cta ccc ggg agc cag cta tat caca lagging ctg cta cac gcc gag gag ttc cac cc cc ttc ctg gca aag atg agg ggg lpro cac ccc gag gag ttc cac cc cc ttc ctg gca aag atg agg ggg lpro cac ccc gag gag ttc cac cct ttc ctg gca aag atg agg ggg lpro cac ccc gag gag ttc cac cct ttc ctg gca aag atg agg ggg lpro cac ccc gag gag ttc cac cct ttc ctg gca aag atg agg ggg lpro cac cct ttc ctg gca aag atg agg ggg lpro cac cct ttc ctg gca aag atg agg ggg lpro cac cct gcg gcg ttg gag cag aac lpro leu Ala Lys Met Arg Gly -15 att ctt aag gta ctg ctc ttc ttc gca gcc gcc ttg gag cag aac lpro leu Leu Lys Val Leu Leu Phe Ser Val Val Ser Gly Leu Glu Gln Asn -10 -5 ccc ttg gcc gct ggc ttc aga ctc ccc cac ccg gg gcc gcc gcc ggc ttc aga ctc ccc cac ccg gg gcc gcc gcc gcc gcc gcc	Mot all all gag gag ctt gag ggt ggc	53
aaa ccc ctg agc ggg ctg ctg aat geg ctg gcc cag gac act ttc cac loop		
### Pro beta Set Gly Deta Leva Asn Ala Leva Ala Gln Asp Thr Phe His -60	-65	
### Pro beta Set Gly Deta Leva Asn Ala Leva Ala Gln Asp Thr Phe His -60	aaa ccc ctg agc ggg ctg ctg aat gcg ctg gcc cag gac act ttc cac	101
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gag gtg cca ccc gag gag ttc cac ccc ttt ctg gca aag atg agg ggg ggg gag gtg cca ccc gag gag ttc cac ccc ttt ctg gca aag atg agg ggg 197 Glu Val Pro Pro Glu Glu Phe His Pro Phe Leu Ala Lys Met Arg Gly  -25 -20 -15  att ctt aag gta ctg ctc ttt ct gta gtc tcc ggc ttg gag cag aac 245 Ile Leu Lys Val Leu Leu Phe Ser Val Val Ser Gly Leu Glu Gln Asn -10 -5 10  ccc ttg gcc gct ggc ttc aga ctc tcc cac ccg gg Pro Leu Ala Ala Gly Phe Arg Leu Ser His Pro 5 10 15  <2210 > 246 <2211 > 211 <2212 > DNA <2213 > Homo sapiens  <220 > <221 > C22 > 70 210  <221 > Sig peptide <222 > 70 162 <223 > Von Heijne matrix score 6 . 30000019073486 seg SLILSPSPRPVLG/FF  <400 > 246 tttggctggg gagacccatc tggactacca aggagaagct atagactact tctactccac caggaaggt atg atg atg atg atg atg atg atg	ggg tac ccc ggc atc aca gag gag ctg cta acg acg acg	
Gag gtg cca ccc gag gag ttc cac ccc ttt ctg gca aag agg ggg 197 Glu Val Pro Pro Glu Glu Phe His Pro Phe Leu Ala Lys Met Arg Gly -25 att ctt aag gta ctg ctc ttt tct gta gtc tcc ggc ttg gag cag aac 245 Ile Leu Lys Val Leu Leu Phe Ser Val Val Ser Gly Leu Glu Gln Asn -10 -5 ccc ttg gcc gct ggc ttc aga ctc tcc cac ccg gg Pro Leu Ala Ala Gly Phe Arg Leu Ser His Pro 5 10 15  <210> 246 <211> 211 <212> DNA <213> Homo sapiens  <220> <221> c22> 70162 <223> Von Heijne matrix score 6.30000019073486 seg SLILSPSPRPVLG/FF  <400> 246 tttggctggg gagacccatc tggactacca aggagaagct atagactact tctactccac caggaaggt ata atg atg atg atg atg atg atg	Gly Tyr Pro Gly Ile Thr Gly Cly Ley Ley 2gc cag cta tat cca	149
gag gtg cca ccc gag gag ttc cac ccc ttt ctg gca aag atg agg ggg 197 Glu Val Pro Pro Glu Glu Phe His Pro Phe Leu Ala Lys Met Arg Gly -20 -15 att ctt aag gta ctg ctc ttt tct gta gtc tcc ggc ttg gag cag aac 245 Ile Leu Lys Val Leu Leu Phe Ser Val Val Ser Gly Leu Glu Gln Asn -10 -5 1 ccc ttg gcc gct ggc ttc aga ctc tcc cac ccg gg Pro Leu Ala Ala Gly Phe Arg Leu Ser His Pro 10 15  <210 > 246 <211 > 211 <212 > DNA <213 > Homo sapiens  <220 > <221 > CDS <222 > 70 210  <221 > Sig_peptide <222 > 70 162 <223 > Von Heijne matrix score 6 . 30000019073486 seq SLILSPSPRPVLG/FF  <400 > 246 tttggctggg gagacccatc tggactacca aggagaagct atagactact tctactccac caggaaggt ata gtg atg atg atg atg atg atg		
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att ctt aag gta ctg ctc ttt tct gta gtc tcc ggc ttg gag cag aac le Leu Lys Val Leu Phe Ser Val Val Ser Gly Leu Glu Gln Asn -10 -5 1  ccc ttg gcc gct ggc ttc aga ctc tcc cac ccg gg	Glu Val Pro Pro Glu Glu Phe His Pro Phe Leu Ala Lvs Met Arg Gly	
att ctt aag gta ctg ctc ttt tct gta gtc tcc ggc ttg gag cag aac  Ile Leu Lys Val Leu Leu Phe Ser Val Val Ser Gly Leu Glu Gln Asn  -10  -5  10  280  Pro Leu Ala Ala Gly Phe Arg Leu Ser His Pro 5  10  15  <210> 246 <211> 211 <212> DNA <213> Homo sapiens  <220> <221> CDS <222> 70210  <221> Sig_peptide <222> 70162 <223> Von Heijne matrix score 6.3000019073486 seg SLILSPSPRPVLG/FF  <400> 246  tttggctggg gagacccatc tggactacca aggagaagct atagactact tctactccac caggaaggt atg atg atg tca aac gtg atg ctg atg cta cag tta cag ccc Met Met Met Ser Asn Val Met Leu Met Leu Gln Leu Gln Pro  -30  -25  -20		
ccc ttg gcc gct ggc ttc aga ctc tcc cac ccg gg Pro Leu Ala Ala Gly Phe Arg Leu Ser His Pro 10  15  15  10  15  280  280  280  280  280  280  280  28	att ctt aag gta ctg ctc ttt tct gta gtc tcc ggg ttg	
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ccc ttg gcc gct ggc ttc aga ctc tcc cac ccg gg Pro Leu Ala Ala Gly Phe Arg Leu Ser His Pro 5 10 15  <2210> 246 <211> 211 <212> DNA <213> Homo sapiens  <220> <221> CDS <222> 70210  <221> sig_peptide <222> 70162 <223> Von Heijne matrix	and bed bed pie Ser var var Ser Gly Leu Glu Gln Asn	
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Met Met Met Ser Asn Val Met Leu Met Leu Gln Leu Gln Pro  -30  -25  -20		
Met Met Met Ser Asn Val Met Leu Met Leu Gln Leu Gln Pro  -30  -25  -20	tttggctggg gagacccatc tggactacca aggagaagct atagactact totactaca	60
Met Met Met Ser Asn Val Met Leu Met Leu Gln Leu Gln Pro -30 -25 -20	Caggaaqqt atq atq tca aac gtg atg ctg atg atg atg	
-30 -25 -20	Met Met Ser Non Vol Mot Vou at a Cag CCC	111
	. 70	
cty org gcg cas for org att ofc tot occ for ocg cgt oca gtg ofg 159	ZJ ZU	
	cty dry gog cas tot org att oto tot occ tot ocg ogt oca gtg otg	159

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 Gly Phe Phe Arg Gln Val His Leu Leu Thr Arg Ser His Phe Ser Arg
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                                          10
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                                                                        211
 Trp
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                                                                        120
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                                                                       180
 tgtattgtta gctgtagtca ccctactgtg ctattgaata ctagagcttg ttccttctgt
                                                                       240
ctaactgt atg att ata ctc att aac caa ctt ctc ttc atc tgt ccc cca
                                                                       290
          Met Ile Ile Leu Ile Asn Gln Leu Leu Phe Ile Cys Pro Pro
          -20
cet cea cee ate tea gee tet agt aac tae cat tit act etc tae etc
                                                                       338
Pro Pro Pro Ile Ser Ala Ser Ser Asn Tyr His Phe Thr Leu Tyr Leu
cat gac att aac ttt ttt agc
                                                                       359
His Asp Ile Asn Phe Phe Ser
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                                                                      120
caagaaacag aaacaaaaca gtcacaaaaa agcataaact gttagcattg atccatgatg
                                                                      180
a atg act gat gta tta ctt caa ttg cta tta aga gtg tgt tct ccc agg
                                                                      229
 Met Thr Asp Val Leu Leu Gln Leu Leu Leu Arg Val Cys Ser Pro Arg
  -15
acc agg g
                                                                      236
Thr Arg
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                                                                       120
totgoataag accagttato coagaacogt tigitgaata ggaagttott tiotoatigo
                                                                       180
 ttgtttgtgg ggactttgtc aaagatcaaa tagttatagg tgtgtggctg tatttcaggg
                                                                       240
tttetttatt ceattteact gatet atg ggt etg ttt ttg tge tge tet tta
                                                                       292
                             Met Gly Leu Phe Leu Cys Cys Ser Leu
                                         -10
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                                                                      120
ggaaaggccc tcctccagaa aatgctagaa aacctgagtg gggagctggg gagggagtag
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tggactetge tteattgtee ceagtetgea cacecetee eccaceacee cactgeattt
                                                                      240
cccagetcag ccaaacttte tgannaagae gggeagagnn etgetgggag atg gga
                                                                      296
                                                        Met Gly
tee tgg gee etg act tgg ete eat eea gea gag get ggg ace agg gtg
                                                                      344
Ser Trp Ala Leu Thr Trp Leu His Pro Ala Glu Ala Gly Thr Arg Val
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cct ttc tgc agc tgg gaa aaa tca gat ggg cgc tct ta
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Pro Phe Cys Ser Trp Glu Lys Ser Asp Gly Arg Ser
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 gtgcatatta tacaaatgat ggatataaaa tttgtttwga ccatwta atg atg ctt
                                                                         60
                                                                        116
                                                      Met Met Leu
 rmw wwr rra aga gga tat cct cat aga act gaa cgt tat gat gga ttt
 Xaa Xaa Xaa Arg Gly Tyr Pro His Arg Thr Glu Arg Tyr Asp Gly Phe
                                                                        164
                 -35
                                                           -25
 tta aaa tat tot gac cca aat gat att gca ttg tca gta ctg tcc ctg
 Leu Lys Tyr Ser Asp Pro Asn Asp Ile Ala Leu Ser Val Leu Ser Leu
                                                                        212
             -20
                                  -15
 gtt att aat ttc tcc tgg agt aga aaa tgc ttt gtt cct tac tat atc
 Val Ile Asn Phe Ser Trp Ser Arg Lys Cys Phe Val Pro Tyr Tyr Ile
                                                                        260
         - 5
 cca ttt aaa cct tac cgv nta cct tac ccc acc gcg gcc cgg g
 Pro Phe Lys Pro Tyr Arg Xaa Pro Tyr Pro Thr Ala Ala Arg
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attccatagt catatttata tatataca cacacatata tatgt atg tat gtg tgt
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                                                                      117
                                                   Met Tyr Val Cys .
ata tat ata trt tta ana gac ctg tat gat ttt ttt ctt ctt gga act
Ile Tyr Ile Xaa Leu Xaa Asp Leu Tyr Asp Phe Phe Leu Leu Gly Thr
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PCT/IB99/00712

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-10 ttt tgt att ttc ttt tct gtc cct gcc ctt caa cct aga aga ctg gg

328

-15

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 aacacttcac tctccaactt ttttgccata ttgacaatca ctttcataat ttcacttatt
                                                                        120
 gacyctgynw haaatcmtgt gaagyhatgc agahcatctg gacacagctt tctccagcag
                                                                        180
 ggatyyatdg ttttgggctt gaaggggttt cacggctttt tctataacaa cg atg gca
                                                                        238
                                                            Met Ala
 tct tca atg ctg waa tcc ttc cag act ttc atg atg ttg act cta ttg
                                                                        286
Ser Ser Met Leu Xaa Ser Phe Gln Thr Phe Met Met Leu Thr Leu Leu
                 -20
                                     -15
ggt ttc cct tcc aaa gct ttg aca ttc att tcc a
                                                                       320
Gly Phe Pro Ser Lys Ala Leu Thr Phe Ile Ser
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                                                                        60
tataaagaag tgtaaacagg aaagccagct gggcctggag ttccaagtgc ccatatttca
                                                                       120
tragetteet etecataaet gtggcaggga caettaaece tteeetgget gtgagaagtt
                                                                       180
attctctgag ggctggtgag caga atg gga aga tct aag agg cag ctc ctt
                                                                       231
                           Met Gly Arg Ser Lys Arg Gln Leu Leu
                           -20
tcc ttg cct ggt tcc ttt atc cct ggg aat tgc agg cca agg att ctg
                                                                       279
Ser Leu Pro Gly Ser Phe Ile Pro Gly Asn Cys Arg Pro Arg Ile Leu
                        - 5
agc aat ggw gaa gwc aga agg aag gg
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                                                                        54
                                         Met Arg Ser Asp Gly Phe
                                         -25
 atc agg ggt ttc tgc ttc tgc ttc ttc cta att ttt ctc ctg cca ccg
                                                                       102
 Ile Arg Gly Phe Cys Phe Cys Phe Phe Leu Ile Phe Leu Leu Pro Pro
                                     -10
ctt cct gcc atg ata ctg agg cct ctg cag cca tgt gga att ata agt
                                                                       150
Leu Pro Ala Met Ile Leu Arg Pro Leu Gln Pro Cys Gly Ile Ile Ser
                                                 10
cca att aaa cct ctt ttt cct ttt ttt t
                                                                       181
Pro Ile Lys Pro Leu Phe Pro Phe Phe Phe
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                                                                       60
caaccatctg taatgtatct stcgtttgag cttgtgggcc atacaattca ttaactag
                                                                      118
atg aat aca ttg tgg aca gca tcc tca cta ccc ctc tct act cac tca
                                                                      166
Met Asn Thr Leu Trp Thr Ala Ser Ser Leu Pro Leu Ser Thr His Ser
    -15
                        -10
caa aga acc atg ata cac tgg aat gtt ttt ctc tgg aat tct ttc tac
                                                                      214
Gln Arg Thr Met Ile His Trp Asn Val Phe Leu Trp Asn Ser Phe Tyr
tct tgt att aaa att ttt ccc c
                                                                      236
Ser Cys Ile Lys Ile Phe Pro
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                                                                         60
 cttcttaaga aagtttttct agactaatgt ctagattaaa cttctttct ttgacaataa
 tgatgcc atg act tgg aca aaa tgc cca ttg cct ctg ggt cct gct ttc
                                                                        120
                                                                        169
         Met Thr Trp Thr Lys Cys Pro Leu Pro Leu Gly Pro Ala Phe
 ttc acc cag tgc tgc ctt att gga ctc ctt gtg cct ctc ctt ggc tgg
 Phe Thr Gln Cys Cys Leu Ile Gly Leu Leu Val Pro Leu Leu Gly Trp
                                                                        217
         -15
                              -10
 gga aat cag aat aca cag tgg tat ccc act tct aag atg cct gat ggg
 Gly Asn Gln Asn Thr Gln Trp Tyr Pro Thr Ser Lys Met Pro Asp Gly
                                                                        265
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                                                                        60
ttattgttaa tctacagaaa tatcctccat tcactttgat atttaaatga catcgtacat
                                                                       120
tttaggtaga gcatttttat gaccactcat tgcttagtct g atg ggg agg agc aat
                                                                       176
                                               Met Gly Arg Ser Asn
gat ttt agg ttt gcc ttt cta aca tgc ttt ctt gga tgg gaa ata gta
                                                                       224
Asp Phe Arg Phe Ala Phe Leu Thr Cys Phe Leu Gly Trp Glu Ile Val
        -25
                            -20
tat ttc ttg gtg ctt ctt cgt gtt tta tac act tta caa tgg ggt ggg
                                                                       272
Tyr Phe Leu Val Leu Leu Arg Val Leu Tyr Thr Leu Gln Trp Gly Gly
    -10
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beg	•	•
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cagcaatccc attgctaggt atataccccc cca tatctgaatc cc atg ttt ctt gca gca ct	aaaaagg aaatcagtat at	gaaagaga 12 att tgg 17
Met Phe Leu Ala Ala Le	u Phe Thr Val Ala Lys	Ile Trp
-10	-5	*
aag caa cct aag tgt tca tca aca aac Lys Gln Pro Lys Cys Ser Ser Thr Asn	aaa tgg aca aag aaa af Lys Tro Thr Lys Lys M	tg tgg 21
1 5	10	et Trp 15
tac ata tac aca atg gag tac tat tca	gcc ata aaa aaa gat ga	at atc 26
Tyr Ile Tyr Thr Met Glu Tyr Tyr Ser		-
ctg tca ttt gca aca ata tgg atg gaa	25 Ctg gag agc att aca th	
Leu Ser Phe Ala Thr Ile Trp Met Glu	Leu Glu Ser Ile Thr Le	eu Ser
35 40	45	
gaa ata agt ggg sca cca aaa gac aaa Glu Ile Ser Gly Xaa Pro Lys Asp Lys	itt ctc atg ttc tca ct	c att 36
50 55	60	iu lie .
tgt gga ag		37
Cys Gly 65		
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gtascccggc catggctctg tagcctcgac ccct	ttgtgc ccccggcccg tct	ccgcgct 120
caccacgeet gegeteteeg eteceacett ettt cettgetgea gee atg gag tet tee act tt	caccita ata cet ata	cgcctct 180 ttc 229
Met Glu Ser Ser Thr Ph	e Ala Leu Val Pro Val	Phe 223
-25	-20	•
gcc cac ctg agc atc ctc cag agc ctc g Ala His Leu Ser Ile Leu Gln Ser Leu V	ig cca gct gct ggt gc	agyc 277
-15 -10	-5	a Xaa l
tct cct		283
Ser Pro		
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 cagcgaggca gtctgttctg gttcacagtc atcaccctca gctttggcta ctacac atg
                                                                       119
                                                                Met
 ggt tgt ctt ctg gcc tca gag tat ccc tta tca gaa cct tgg gcc cct
                                                                       167
 Gly Cys Leu Leu Ala Ser Glu Tyr Pro Leu Ser Glu Pro Trp Ala Pro
                             -70
 ggg ccc ttc act cag tac ttg gtg gac cac cat cac acc ctc ctg tgc
                                                                       215
 Gly Pro Phe Thr Gln Tyr Leu Val Asp His His His Thr Leu Leu Cys
                      - -55
                                             -50
 aat ggg tat tgg ctt gcc tgg ctg att cat gtg gga gag tcc ttg tat
                                                                       263
Asn Gly Tyr Trp Leu Ala Trp Leu Ile His Val Gly Glu Ser Leu Tyr
                     -40
                                         -35
gcc ata gta ttg tgc aag cat aaa ggc atc aca agt ggt cgg gct cag
                                                                       311
Ala Ile Val Leu Cys Lys His Lys Gly Ile Thr Ser Gly Arg Ala Gln
                -25
cta ctc tgg ttc cta cag act ttc ttc ttt ggg ata gcg tct ctc asc
                                                                       359
Leu Leu Trp Phe Leu Gln Thr Phe Phe Phe Gly Ile Ala Ser Leu Xaa
            -10
atc ttg att gc
                                                                       370
Ile Leu Ile
    5
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tggttattat ccttcattct gttgatgtga tgtatcacat ttattgattt gcatatgttg
                                                                      120
aacceteett geatecetgg aatgatteet aetteattat agtgtataat etttttg
                                                                      177
atg tgc tgt tgg att tgg gtt gct agt att ttg ttg aga att ttt gca
                                                                      225
Met Cys Cys Trp Ile Trp Val Ala Ser Ile Leu Leu Arg Ile Phe Ala
                        -10
tot gtg tta atc agg gat att tac ctg tgg ttt tot ttt ttt ttt t
                                                                      274
Ser Val Leu Ile Arg Asp Ile Tyr Leu Trp Phe Ser Phe Phe Phe
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                                                                        60
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                                                                       120
 tataaattac ctctcaaaca aatgggccat tcagaarnrg gctcagagtg aattagctgg
                                                                       180
 aggggttgtc aagggtcata gtttttactg ctttgaagag attatcactg g atg att
                                                                       237
                                                           Met Ile
 tee tea cat tta tat aac tte agt ete etg tte ttt kta ete tgg etg
                                                                       285
 Ser Ser His Leu Tyr Asn Phe Ser Leu Leu Phe Phe Xaa Leu Trp Leu
     -20
                         -15
                                             -10
 agg tac aag gaa tca gga aga ggc aac tgt gag gaa gga gca ttc
                                                                       333.
 Arg Tyr Lys Glu Ser Gly Arg Glu Gly Asn Cys Glu Glu Gly Ala Phe
 tcc agg tgg
                                                                       342
 Ser Arg Trp
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g atg ggg tgg cag cga ctc cta ctg ctg cct cgg cct cct gcc agt aca
                                                                      109
  Met Gly Trp Gln Arg Leu Leu Leu Pro Arg Pro Pro Ala Ser Thr
                              -10
ggt gca tcg aat gca acc agg rrg cca aag agk ttg tac cga grc tat
                                                                      157
Gly Ala Ser Asn Ala Thr Arg Xaa Pro Lys Xaa Leu Tyr Arg Xaa Tyr
aac cac ggt gtg ctg aag ata acc atc tgt aaa tcc tgc cag aaa cct
                                                                      205
Asn His Gly Val Leu Lys Ile Thr Ile Cys Lys Ser Cys Gln Lys Pro
                20
                                    25
gta gac aaa tat atc gag tat gat cct gtt atc atc ttg awk aat gct
                                                                      253
Val Asp Lys Tyr Ile Glu Tyr Asp Pro Val Ile Ile Leu Xaa Asn Ala
            35
ata ttg tgc aaa gct cad gcc tac agr cat att ctt ttc aat act caa
                                                                      301
Ile Leu Cys Lys Ala Xaa Ala Tyr Arg His Ile Leu Phe Asn Thr Gln
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55
  ata aat aac aaa ctg cct att tta ttg gca ttt tta cct tcc tgt ggv
  Ile Asn Asn Lys Leu Pro Ile Leu Leu Ala Phe Leu Pro Ser Cys Gly
                          70
                                               75
  dga acg gcc cat gac ggc aaa aaa aag ccc aac ttc att ttg ctg ctg,
                                                                        397
  Xaa Thr Ala His Asp Gly Lys Lys Pro Asn Phe Ile Leu Leu
                      85
  aaa sat tat tat tat cta gct acg gaa aac
                                                                        427
  Lys Xaa Tyr Tyr Tyr Leu Ala Thr Glu Asn
                  100
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                      Met Ala Ala Gly Val Ser Leu Leu Ala Leu Val
                                      -15
gtt cgg gtc atc cta tcc acc gcc atc ctt tgc ccg agt ggg gcc agt
Val Arg Val Ile Leu Ser Thr Ala Ile Leu Cys Pro Ser Gly Ala Ser
                                                                       100
cgg cgc cag agg agt tct gag gtt gag tgg gga act gat tcg g
Arg Arg Gln Arg Ser Ser Glu Val Glu Trp Gly Thr Asp Ser
                                                                       143
    10
                         15
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                         Met Asn Pro Leu Phe Trp Leu Ile Leu Cys
                         -15
tct ggg tta tta tgt aac aag tca ttt
                                                                       79
Ser Gly Leu Leu Cys Asn Lys Ser Phe
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                                                                        60
atg aga ggg gct tgg ata agt ata ttt ctt tct tct cta tct ctc tct,
                                                                       108
Met Arg Gly Ala Trp Ile Ser Ile Phe Leu Ser Ser Leu Ser Leu Ser
             -15
                                 -10
ctc tct ctt ttt t
                                                                       121
Leu Ser Leu Phe
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                                                                        60
aaaaggaaaa aatattattt ccaaagagta agttatgaag ccatgttaga aacccatatg
                                                                       120
acaatatgaa tttcttttat ctgtcaatct caaggtagaa ttcctcatat ttctgataat
                                                                       180
gccaaatacc atgaa atg tct caa aaa aga ctt gac ttt ata tac cag ttg
                                                                       231
                 Met Ser Gln Lys Arg Leu Asp Phe Ile Tyr Gln Leu
                                 -20
                                                      -15
ttt gtc ttg ctg cct cac ttc ttc ctt tct ttt ctt tct ccc ttt tat
                                                                       279
Phe Val Leu Leu Pro His Phe Phe Leu Ser Phe Leu Ser Pro Phe Tyr
        -10
                            -5
ctg cac cca tgg g
                                                                       292
Leu His Pro Trp
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Met Tyr Leu Tyr Leu Leu Ser Ile Cys Met Ser Ser Leu Lys Lys Cys -30 -25 -20	49
cta ttc aag ttc tta gcc cac ttt tta atc ggg tta aca gtt tgt ttt Leu Phe Lys Phe Leu Ala His Phe Leu Ile Gly Leu Thr Val Cys Phe -15 -10 -5	97
ggt gag ggr wgg cta atg agt tat agg agt tct tat tta tta ctt aaa Gly Glu Gly Xaa Leu Met Ser Tyr Arg Ser Ser Tyr Leu Leu Leu Lys 1 5 10 15	145
gga cca ccg ggg g Gly Pro Pro Gly	158
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catatttatt ttgagataat taacgaagac gttaaataaa gccagactgc actgaccct	120 180
ggggcgcc atg cga gac ccc ctc gcg gac atg gta cac agt tat tta tca Met Arg Asp Pro Leu Ala Asp Met Val His Ser Tyr Leu Ser -25	230
tog tot tig tic atg god ott oca oca gig oig ago toa cat god ago	278
Ser Ser Leu Phe Met Ala Leu Pro Pro Val Leu Ser Ser His Gly Ser -15 -10 -5	
agg aac ctg aga atc tgg ggg agt cca ttt ggt gga gcg ctg act aag	326
Arg Asn Leu Arg Ile Trp Gly Ser Pro Phe Gly Gly Ala Leu Thr Lys  5 10 15	
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-15 gg ctg tgt ctg cca tgc tcc ctg tgt gtg tcc cag ctc ctt ccc tct	105
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regerriwe twitterawer tgaggitt atg tet t	ta aac gag tta agc ata Leu Asn Glu Leu Ser Ile -15	172
ct gat tta tta ccc agc tca tcc ttt gct la Asp Leu Leu Pro Ser Ser Ser Phe Ala 10 -5	aat ccc aag ctg agt ggg Asn Pro Lys Leu Ser Gly	220
cg att tct atc tcg gtc act tca gct ggt ro Ile Ser Ile Ser Val Thr Ser Ala Gly 10 15	tet eet eee aag eea	265
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                                                                       118
                                                       Met Lys Asp
tta ctt ggc act gcc ttt ctg gag gga agt tta gca gca tat ctc acc
                                                                       166
Leu Leu Gly Thr Ala Phe Leu Glu Gly Ser Leu Ala Ala Tyr Leu Thr
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                                 Met Ala Asn Asp Ile Lys His Leu
ttc atg tgc tta ttg acc ata tgt ata tct tct ttg gag aaa ctt cca
                                                                       162
Phe Met Cys Leu Leu Thr Ile Cys Ile Ser Ser Leu Glu Lys Leu Pro
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Phe Phe Phe Phe
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Val Leu Gly Gln Ile Leu Val Ser Val Ala Gly Trp Ser Leu Phe Ser 1 5 10	152
ctg aat gtc atc tct ctt acc tgt gtt tca gtg gct ttt gct gtg gcc Leu Asn Val Ile Ser Leu Thr Cys Val Ser Val Ala Phe Ala Val Ala 15 20 25	200
tgg ttt tta cct atg cca cag aag agc ctc ttc ttt cac cac att cct Trp Phe Leu Pro Met Pro Gln Lys Ser Leu Phe Phe His His Ile Pro 30 35 40 45	248
tct acc tgc cag aga gtg aat ggc atc aag gta caa aat ggt ggc att Ser Thr Cys Gln Arg Val Asn Gly Ile Lys Val Gln Asn Gly Gly Ile, 50 55 60	296
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                                 Met Asn Cys Val Thr Leu Ile Gln
                                     -20
gcc ttg tcc ctc tgg gcc tca gtt tcc cca agc tgg atg tgt cgt ccc
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Ala Leu Ser Leu Trp Ala Ser Val Ser Pro Ser Trp Met Cys Arg Pro
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Pro Ala Ser Phe Ile Ile Thr Thr Thr Thr Thr Cys Gly
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ctaccagaat cctgcctcac tggagcagag gatgccagca tcagccggga accactcctg
                                                                      180
tgctaaaacc gccttggtgg cctgtggctt gaggtcttga tgcggatgaa gccggagga
                                                                      239
atg ttg tct ctc ctc agt ctc atg gca agg act gat ctt gtt ttc tgt
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Met Leu Ser Leu Leu Ser Leu Met Ala Arg Thr Asp Leu Val Phe Cys
    -15
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tcc cca cgg g
                                                                      297
Ser Pro Arg
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						-30					-25						
gtg	gcc	gtt	acg	gcc	gaa	aag	atg	gcg	gto	ttg	gca	cct	cta	att	gct		97
	Ala	Val	Thr	Ala		Lys	Met	Ala	Val	Leu	Ala	Pro	Leu	Ile	Ala		
-20					-15					-10					-5		
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Leu	vaı	Tyr	ser	vai 1	Pro	Arg	Leu	ser	Arg	Trp	Leu	Ala		Pro	Tyr		
t 2.0	a++	a+ a	tca	_	at a	ata	+ -+	5					10				
Tyr	Len	Len	Ser	λla	Leu	Leu	COT	31.	gcc	Phe	cta	ctc	gtg	agg	aaa	•	193
- 7 -	Deu	15	001	AIG	Deu	Deu	20	WIG	Ала	Pne	ьец	ьеu 25	vai	Arg	Lys		
ctq	ccq		ctc	tac	cac	aat		CCC	acc	caa	cac	722	Ga C	aat.	226		241
Leu	Pro	Pro	Leu	Cys	His	Glv	Leu	Pro	Thr	Gln	Ara	Glu	Aen	637	λen		241
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Pro	Cys	Asp	Phe	Asp	Trp	Arg	Glu	Val	Glu	Ile	Leu	Met	Phe	Leu	Ser		
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Ala	Ile	Val	Met		Lys	Asn	Arg	Arg		Ile	Thr	Val	Glu	Gln	His		•
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Phe	Ara	Len	Asp	Tle	Ara	Met	Glv	Len	Len	tac Tyr	atc	aca	CEC	tgc	ata		433
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Val	Phe	Leu	Met	Thr	Cys	Lys	Pro	Pro	Leu	Tyr	Met	Glv	Pro	Glu	Tvr	٠.	401
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Ile	Xaa	Tyr	Phe	Asn	Asp	Lys	Thr	Ile	Asp	Glu	Glu	Leu	Glu	Arg	Asp		
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Lys	Arg	Val			Ile	Val	Glu	Phe	Phe	Ala	Xaa	Trp	Ser	Asn	Asp		
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tgc	caa	tca	בבכ	gcc	cct	atc	tat	gct	gac	ctc	tcc	ctt	aaa	tac	aac		625
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Cyc	aca Th~	299	T.ell	aat Nen	Dho	999	aag	grg	gat	gtt	gga	cgc	tat	act	gat		673
Cys	1111	175	Deu .	usii	PIIC		шуs 180			Val				Thr	Asp		
att	agt		caa	tac	222			202	+ = =	ccc	ctc	182					
Val	Ser	Thr	Ara '	Tvr	Lvs	Val	Sor	Thr	Car	Pro	LOU	mb-	Tue	Caa	CEC		721
• • • • • • • • • • • • • • • • • • • •	190	1111		- ] -		195	361	1111	261	PIO	200	Inr	гÀг	GIn	Leu		
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Met Pro Ser Val Pro Leu Ser Ser Asp Pro Leu Pro Thr His Thr Thr
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gca ttc tca ccc gca agc acc ttt gaa aga gaa aat gac ttc tca gag
                                                                      367
Ala Phe Ser Pro Ala Ser Thr Phe Glu Arg Glu Asn Asp Phe Ser Glu
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acc aca act tet ett agt eca gae aat act tee acc caa gta tee eeg
                                                                      415
Thr Thr Thr Ser Leu Ser Pro Asp Asn Thr Ser Thr Gln Val Ser Pro
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                                        65
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                                                                      463
Asp Ser Leu Asp Asn Ala Ser Ala Phe Xaa Thr Thr Gly Val Ser Ser
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Val Gln Thr Pro Xaa Leu Pro Thr His Ala Asp Ser Gln Thr Pro Ser
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Ala Gly Thr Asp Thr Gln Thr Phe Ser Gly Ser Ala Xaa Met Gln Asn
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tca acc cta ccc cag gca gca atg cta tct cag atg tcc cag gag aga
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	-15	-				-10					- 5		•		
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ccc act g	gt gtt	tca	tca	gta	cag	acc	ccc	cag	99				*	•	251
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Lys Leu Le	u Ala	Phe	Gly	Phe	Ala	Phe	Len	Asn	Thr	Glu	Val	Dhe	yes		223
-10			-5					1	1111	Ų.Lu	·Vui	5	vai	•	
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Thr Gly Gl	n Ser	Pro	Thr	Pro	Ser	Dro	Thr	994	1/21	ec-	Cox	yca v-1	Cay		271
	10					15	- 11I	Gry	vaı	ser		vaı	GIN		
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Thr Pro His	z T.eu	Dro	Thr	uic	yla Nla	yac	ccg	cay	acg	CCC	CCC	gct	gga		319
Thr Pro Hi	5 Deu	PIO	1111	nis	Ara	Asp	ser	GIn	Thr		Ser	Ala	Gly		
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Thr Asp Th	r Gin	Inr	Pne	ser	GIA	Ser	Ala	Xaa		Gln	Asn	Ser	Thr		
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                                                                       120
 gccaggag atg aca gca ctg ggg ttt gtt ctg tta gct cca cgt ggc tgg
                                                                       170
          Met Thr Ala Leu Gly Phe Val Leu Leu Ala Pro Arg Gly Trp
          -15
                              -10
ggg agc ctc aca gtc atg gtg gaa ggc aag gaa gag caa gtc acg tct
                                                                       218
Gly Ser Leu Thr Val Met Val Glu Gly Lys Glu Glu Gln Val Thr Ser
                                         10
tac acg gat ggc agc agg caa aga gac agc aat ttt
                                                                       254
 Tyr Thr Asp Gly Ser Arg Gln Arg Asp Ser Asn Phe
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tggagactgc tgcacggact ctggaaccat gaacatattt gatcgaaaga tcaactttga
                                                                      120
tgcgctttta aaattttctc atataacccc gtcaacgcag cagsrcctga agaagatttc
attactgtct tcagaaaact catgatgatc ctggccatga atg aaa agg ata aga
                                                                      235
                                            Met Lys Arg Ile Arg
aga aag aga aga aat gaa gtg acc atc cag cct ttc cca att aga ctt
                                                                      283
Arg Lys Arg Arg Asn Glu Val Thr Ile Gln Pro Phe Pro Ile Arg Leu
                -30
                                    -25
cet etc ett eca ece etc att tec ttt ttg eac aca tta eag gtg gtg
                                                                      331
Pro Leu Leu Pro Pro Leu Ile Ser Phe Leu His Thr Leu Gln Val Val
                                -10
tgt tct gtg ata atg aaa agc atc aga aaa gct ttt gta ctt tgt ggt
                                                                      379
Cys Ser Val Ile Met Lys Ser Ile Arg Lys Ala Phe Val Leu Cys Gly
ttc ctc tat ttt gaa ttt ttt gat caa aaa ctg at
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Phe Leu Tyr Phe Glu Phe Phe Asp Gln Lys Leu
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<211> 334

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PCT/IB99/00712

165

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tectattata gtacaggaaa ggteetteet gteaaaggea aaateaetta tgattgte	ct 6
cccatctctc ttgccttttc aaggactttg agcct atg ctg cca ctg ctt cat	
Met Leu Pro Leu Leu His	17.
-20	
tgt ttt ttt ttk gtt kgt ttg ttt kgt ttk gtt ttk gtt twa ama gca	
Cys Phe Phe Xaa Val Xaa Leu Phe Xaa Xaa Val Xaa Xaa Ala	22
	į
get tta ttg aga tat aat yea agt ata eag kgt gge egg gea eag kge	26
Ala Leu Leu Arg Tyr Asn Xaa Ser Ile Gln Xaa Gly Arg Ala Gln Xaa	· '
ctc ama cct gwa atc cca gma ctt tgg gag act aag gma ggc aga tta	31
Leu Xaa Pro Xaa Ile Pro Xaa Leu Trp Glu Thr Lys Xaa Gly Arg Leu	i
20 25 30	
ctt gag cct agg aat tt	334
Leu Glu Pro Arg Asn	
35	
010 005	
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aggtgagccg gtcctgcgga gttgtgccga gtgcctgctg cagtctcatt tccagttc	ct 180
ccatgacgtg gcaagtgaag acaggaatga aaggratgta aagcagcttt tctctgaa	ga 240
gaagaagaga gagagacaca gccaagaccg aggctgggcc aag atg gtg tct gtg	295
Met Val Ser Val	
-20	
ttt cga agc gag gag atg tgt ttg tca caa ctg ttt ctc cag gtg gaa	2 4 2
Phe Arg Ser Glu Glu Met Cys Leu Ser Gln Leu Phe Leu Gln Val Glu	343
-15 -10 -5	
get gea tat tge tgt gtg get gag ete gga ga	
Ala Ala Tyr Cys Cys Val Ala Glu Leu Gly	375
1 5	
210. 206	
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 aagaagagte tgttatgatg tgtaatacca atttetggag gge atg get ete
                                                                         60
                                                                        115
                                                  Met Ala Ala Leu
 cga agt act cta aca tgg aca gaa gtc gtg ggc tgg tgg agt gtt gcg
 Arg Ser Thr Leu Thr Trp Thr Glu Val Val Gly Trp Trp Ser Val Ala
                                                                        163
                  -20
                                      -15
 tog ctg ctt agt gat gtg gca gca tgg tgg cca ccg cac tcc acc tca
 Ser Leu Leu Ser Asp Val Ala Ala Trp Trp Pro Pro His Ser Thr Ser
                                                                        211
                                  1
 aca cgg gga ggg gta
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 Thr Arg Gly Gly Val
     10
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                                                                       113
                                 Met Asn Ala Leu Val Asp Gly Lys
                                                 -40
cgg ctt asa krg tgc ata cgc tat ttc gat tct atc tca cta tat tct
Arg Leu Xaa Xaa Cys Ile Arg Tyr Phe Asp Ser Ile Ser Leu Tyr Ser
                                                                       161
    -35
                        -30
                                             -25
aag gca agt tta agt tgt tgt tta gtg tgt gtg ttt act tgt tca ttg
Lys Ala Ser Leu Ser Cys Cys Leu Val Cys Val Phe Thr Cys Ser Leu
                                                                      209
cta gct ttc ttc agc cca tgc ac
                                                                      232
Leu Ala Phe Phe Ser Pro Cys
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WO 33/33031			PC1/1B99/003
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gta cag cca ggg cgg tcc Val Gln Pro Gly Arg Ser 15	ctc aga ctc t Leu Arg Leu S 20	er Cys Arg Thr S	ct gga ttc 144 Ger Gly Phe
gcc ttt gat gat tat aat Ala Phe Asp Asp Tyr Asn 30	ttg agt tgg g Leu Ser Trp V	to ege cag get o	ca qqq aaq 192
ggg ctg gag tgg gta ggt Gly Leu Glu Trp Val Gly 45	ttc att aga a Phe Ile Arg S 50	gc aaa cct tat o	gt gag aca 240 ly Glu Thr
aca acg tac gcc gcg tgg Thr Thr Tyr Ala Ala Trp 60 65			258
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cag agt ttc act cht gwt of Gln Ser Phe Thr Xaa Xaa 1		-10	-5 139
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cttccattct ccatgttgtc tttttattct cttgatggta ttctttgaaa tacaaaartk

tttat gataa	atcc	tg a	acaa tttt	agtt wttg	ca g	tta	ttta	t tt	attt	attg taga	ga	tg g	gg t	ct c Ser F	cc t ro T	at	360 416
gtt g Val /	Ala 1	His	-15	GIY	Leu	Glu	Leu	Leu -10	Thr	tca Ser	agt Ser	gat Asp	cct Pro		20 tcc Ser	!	464
ttg g	Ala S	cc Ser	caa Gln	gtg Val	ctg Leu	gga Gly 5	ata Ile	cat His	tm			•					493
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tcgtg	gača	c a	cccc	cag	atg	cat	ctt	tac	act	cat His	gta	tgc	tgg	ctc	act	ac	111
ctc a Leu T	hr L	eu i	Ala : -5	His	Ser	His	Ser	Leu 1	Thr	His	Thr	His 5	Thr	ctc Leu	Thr	.•	159
ccc ag Pro So	er H	ac a	aca Thr	cgt Arg	aca Thr	cac His 15	tca Ser	cat His	acg Thr	tgt Cys	gct Ala 20	tgc Cys	cta Leu	cac His	gca Ala		207
cac a His Ly 25					٠												214
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gttctcatta cctgttccca cgtgccagcc tccttttctg ttgtgnmmaa gtcaagtttg
                                                                      300
gtaaa atg agg ctt tcc tta acc ttt tat cat ttc cca ctg tgt tgg gga
      Met Arg Leu Ser Leu Thr Phe Tyr His Phe Pro Leu Cys Trp Gly
                           -10
cac cag gct gtg ccc acg tgg tgg saa rgc atc att caa cct tgt cac
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His Gln Ala Val Pro Thr Trp Trp Xaa Xaa Ile Ile Gln Pro Cys His
tgt gcc ctc tgc act tct gca gaa ggt gtg caa tca cat atc ata agt
Cys Ala Leu Cys Thr Ser Ala Glu Gly Val Gln Ser His Ile Ile Ser
gna att tac aga
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Xaa Ile Tyr Arg
        35
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                                                                      113
                             Met Asn Val Leu Ile Ile Val Phe Val
gca ttt gct ttt ggg ttc ytg gtc atg aag tct ttg ctt aag cca atg
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Ala Phe Ala Phe Gly Phe Leu Val Met Lys Ser Leu Leu Lys Pro Met
tcg aga agg gtt ttt ctg atg tta tct tct agg att ttt atg gtt tca
                                                                      209
Ser Arg Arg Val Phe Leu Met Leu Ser Ser Arg Ile Phe Met Val Ser
ggt ctt aga ttt aag tcc ttg atc cat ctt gag ttg att ttt gta tat
                                                                      257
Gly Leu Arg Phe Lys Ser Leu Ile His Leu Glu Leu Ile Phe Val Tyr
aag ttg aga gat gag gat cca gtt tca ttc ttc tac atg tgg ctt gcc
                                                                      305
Lys Leu Arg Asp Glu Asp Pro Val Ser Phe Phe Tyr Met Trp Leu Ala
aat tat ccc agc acc att tgt tg
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Asn Tyr Pro Ser Thr Ile Cys
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                                                                       180
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                                                                       240
ag atg ggg tot ege oot gtt toe gak get ggt ete gaa ete etg gee
                                                                       287
   Met Gly Ser Arg Pro Val Ser Xaa Ala Gly Leu Glu Leu Leu Ala
        -20
                           -15
                                                -10
tog age aat tot tot goe ttg coe tte caa tgt tot ggg att aca gge
                                                                       335
Ser Ser Asn Ser Ser Ala Leu Pro Phe Gln Cys Ser Gly Ile Thr Gly
atg agc crc cac acc cta gcg q
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Met Ser Xaa His Thr Leu Ala
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tgtgggggrg artatagtka cgaaaaagrk tattgtttcc cataatgcct ggtattgtat
                                                                      180
taagtacttt gcatacagta gggcatttca ttgtcccagt gatcctcctg caaagtaggt
                                                                      240
acaattatct tcaatttaca aatgaggaaa ccaagctctc ttcaagctga taagatgctg
                                                                      300
aactgagatt tgaaccaagt ccctctgccc ctaagagccc ctacccctag ctgctactat
                                                                      360
atgctgtacc catctaagct ttgtgaaata rccttgttcc actgcagaga ag atg ttg
                                                                      418
tgt cac cta tct cta gta ttt ctt ggc ktt ggg cag ttc tgg agt caa
                                                                      466
Cys His Leu Ser Leu Val Phe Leu Gly Xaa Gly Gln Phe Trp Ser Gln
    -10
                        -5
aat g
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Asn
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WO 99/53051 PCT/IB99/00712 174 <210> 312 <211> 187 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 98..187 <221> sig peptide <222> 98..148 <223> Von Heijne matrix score 5.59999990463257 seq FMCLFAICISSNA/KC <400> 312 aagtttgttt ttgttggtgg tggtgatagt ttcttatatt ctattccata aagtatgaaa 60 tggaggctcc ttgtgatttt taatttgcac ttctgta atg act aat ctt ttc atg 115 Met Thr Asn Leu Phe Met tgc ttg ttt gcc atc tgt ata tct tct aat gcg aag tgt ctg ttt agt 163 Cys Leu Phe Ala Ile Cys Ile Ser Ser Asn Ala Lys Cys Leu Phe Ser -10 -5 ctt ttt cct ttt ttt att gag ggg 187 Leu Phe Pro Phe Phe Ile Glu Gly <210> 313 <211> 237 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 93..236 <221> sig\_peptide <222> 93..173 <223> Von Heijne matrix score 5.59999990463257 seq CVLFTLLVSTRSG/RS <221> misc\_feature <222> 111 <223> n=a, g, c or t <400> 313 ttgcttagga ttttctaaaa gattacataa aatactgttg aaaagatgat tgcatacaaa 60 acataatctg ttcattgtta aacgtatacg aa atg ttg gga tac atc tgg naa 113 Met Leu Gly Tyr Ile Trp Xaa caa gac aaa gtc ttt gct aat tgt gtt cta ttt acg ctc tta gtg tct 161 Gln Asp Lys Val Phe Ala Asn Cys Val Leu Phe Thr Leu Leu Val Ser -20 -15 aca aga tcc ggg aga tcg cgs gcg ggt tgt gcc tgg agg tgg agg gga 209 Thr Arg Ser Gly Arg Ser Arg Ala Gly Cys Ala Trp Arg Trp Arg Gly

237

15

aga tgg tca gta gga cag aag ggc hgg g

20

Arg Trp Ser Val Gly Gln Lys Gly Xaa

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                                                                        60
aagaggggaa agcccagggg tacaggaggc ctctgggtga aggcagaggc taacatgggg
                                                                       120
ttcggagcga ccttggccgt tggcctgacc atctttgtgc tgtctgtcgt cactatcatc
                                                                       180
atotgottca cotgotoctg otgotgoott tacaagacgt googcogacc acgtooggtt
                                                                       240
gtcaccacca ccacatccac cactgtggtg c atg nnc ctt atc ctc agc ctc
                                                                       292
                                    Met Xaa Leu Ile Leu Ser Leu
                                    -15
caa gtg tgc cgc cca gct acc ctg gac caa gct acc agg gct acc aca
                                                                       340
Gln Val Cys Arg Pro Ala Thr Leu Asp Gln Ala Thr Arg Ala Thr Thr
cca tgc cgc cta cgg g
                                                                       356
Pro Cys Arg Leu Arg
    10
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                                                                       54
                                           Met Cys His Arg Arg
tgg ctg cac cta tca acc cgt cat cta ggt ttt aag ccc cgc atc cat
                                                                      102
Trp Leu His Leu Ser Thr Arg His Leu Gly Phe Lys Pro Arg Ile His
                            -25
tac gta ttt gtc tta atg ctg tcc ctc ccc ttg ccc ccc acc ccc caa
                                                                      150
Tyr Val Phe Val Leu Met Leu Ser Leu Pro Leu Pro Pro Thr Pro Gln
    -15
                        -10
                                             - 5
cag gcc ctc ggg
                                                                      162
Gln Ala Leu Gly
1
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<400> 316
taagctgaaa aagaatataa aaattaaaga gaaattgaaa atctaagtct tgcagtgaga
                                                                     60
atgaccagaa atcgtttccc tctctggggg gttcctgttt aatatgaaag tcctcttaac
                                                                    120
aagcgtggac agaggaagtt ttaggtttga tttgaacttc atgtacatga catatttcat
                                                                    180
240
ttccattgct gcttccaaga tactcctgga atctgagatt accttttatc ctcttg atg
                                                                    299
gac cat gtt gtt att ttt gtc att ttc cct gca gct ctt ctg ctt tgc
                                                                    347
Asp His Val Val Ile Phe Val Ile Phe Pro Ala Ala Leu Leu Cys
            -15
                                -10
tgg gga gga ctc atc ccc cta tgc atc atc tac ccc ccg ata gct gac
                                                                    395
Trp Gly Gly Leu Ile Pro Leu Cys Ile Ile Tyr Pro Pro Ile Ala Asp
                                           10
aca gtt ggg
                                                                    404
Thr Val Gly
15
<210> 317
<211> 450
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<222> 359..448
<221> sig peptide
<222> 359..433
<223> Von Heijne matrix
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      seq LIIILXFDIYSLA/FI
<221> misc_feature
<222> 323,410
<223> n=a, g, c or t
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tatgtetttt gaatttgtga tgtacatatt aacagtagat taagttgaaa taataaaatc
                                                                     60
tgtattgttt atgatttatc agttatatga tgagtagaat atagtctatt gtggscmagt
                                                                    120
gtgtatatat aacataaaca atacattaac ccaattttgt gtgaaaatta ttttgggacc
                                                                    180
tagtagettt ettggteaca acettteaaa caaacaaatt ttttttaaat taattttte
                                                                    240
ccttaataaa gaaaacaatt cctcaatgtg taatagcaaa taccttttaa caggtcatat
atcatcaatg Ctttctttga aancgtactg atgcttacaa gatgctttac gagtaaag
                                                                    358
atg ctt aca aat ctt ttc ttt caa gta gct cat cct ctg atc att att
                                                                    406
Met Leu Thr Asn Leu Phe Phe Gln Val Ala His Pro Leu Ile Ile
                                      -15
ctg ntg ttt gat atc tac tcc cta gca ttt atc cat gac gtg gg
                                                                    450
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177
Leu Xaa Phe Asp Ile Tyr Ser Leu Ala Phe Ile His Asp Val
                 -5
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<211> 395
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<222> 313..393
<221> sig_peptide
<222> 313..354
<223> Von Heijne matrix
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      seq LFGLRGMLPLTQQ/AP
<400> 318
aatogaaaac agcaaatcac acaactgtta aaaatatttt vtgtttacaa agccaagcca
aaattttatg ttttcctccc caaactttga tataaacact aacatttttt agcatgtata
                                                                       120
aacatcatta ttaaccagtg teetattaaa acteetttte tatgatagaa tqtetgttre
                                                                       180
ttttaggtgg ataaggccta gatgattggc ctctaccagc atcctcatct ctgtccctga
                                                                       240
tgcccagctt carecteget cetgyatget ggaccgette agtghagete teagacttge
                                                                       300
totgtgtotc ac atg cty ttt ggc tta cgt gga atg ctc cca ctc acc cag
                                                                       351
              Met Leu Phe Gly Leu Arg Gly Met Leu Pro Leu Thr Gln
caa gct ccc att cct cat tta aga tgt aaa ttg agt gtc acc tc
                                                                       395
Gln Ala Pro Ile Pro His Leu Arg Cys Lys Leu Ser Val Thr
<210> 319
<211> 257
<212> DNA
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<221> CDS
<222> 20..256
<221> sig_peptide
<222> 20..82
<223> Von Heijne matrix
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      seg ACVYACVCASVSA/CV
<400> 319
catctgtgtg tgcgtgtgt atg cgt gtg tgt atg cgt ctg tgt gca tgt gtg
                                                                       52
                     Met Arg Val Cys Met Arg Leu Cys Ala Cys Val
                         -20
                                              -15
tat gcg tgt gtg tgc gca tca gtg tct gca tgt gtg tat rtg tgt gta ·
                                                                      100
Tyr Ala Cys Val Cys Ala Ser Val Ser Ala Cys Val Tyr Xaa Cys Val
-10
                    -5
tgt atg tst gtg cgc gcg cat ctg tgt gtg tgc atg tgt gta tgt atg
                                                                      148
Cys Met Xaa Val Arg Ala His Leu Cys Val Cys Met Cys Val Cys Met
           10
                                15
tgt gtg cat etc tgt gtg tge atg tgt gta tgt gtg tgt gea tet qtg
                                                                      196
Cys Val His Leu Cys Val Cys Met Cys Val Cys Val Cys Ala Ser Val
        25
                            30
tgt gtg tgc atg tgt gca tgc gtg tgt atg tgt gtg tgc gtg cgt gca
Cys Val Cys Met Cys Ala Cys Val Cys Met Cys Val Cys Val Arg Ala
    40
                        45
                                            50
tct gtg tgt gtg c
                                                                      257
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Ser Val Cys Val
<210> 320
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<221> CDS
<222> 256..324
<221> sig_peptide
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<223> Von Heijne matrix
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<400> 320
accacgeete etecaagtee cagegaacee gegtgeaace tgteeetaaa aaagecaaag
cagteactet ttacetecca etttecetee teccageett tggcaaceae taatetaett
                                                                       120
tecgtgtata tggatttace tatteaggae attteatatg teetttggtg actggettet
                                                                       180
ttcactttgc acaatgtttt taaggttcat tcctgtcata gtgtgtgtca gtacgaaccc
                                                                       240
ctccttaacc atcta atg gtt atc acc tct aat agt tat ctc ata gcc aat
                                                                       291
                 Met Val Ile Thr Ser Asn Ser Tyr Leu Ile Ala Asn
                     -20
                                          -15
ctt gtt tta ttt ata tct atc gcc gcc ctc cgg g
                                                                       325
Leu Val Leu Phe Ile Ser Ile Ala Ala Leu Arg
                -5
<210> 321
<211> 201
<212> DNA
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<222> 31..201
<221> sig peptide
<222> 31..183
<223> Von Heijne matrix
      score 5.5
      seg LSLHASLVTKAFS/IN
catcacaaga acccagagtg gaattctggg atg gaa gag ctg gac aga aag tgg
                                                                        54
                                 Met Glu Glu Leu Asp Arg Lys Trp
                                     -50
                                                          -45
aga gag aag gtc ctc cca gcg gca aag cta att aaa agg aga aac ctg
                                                                       102
Arg Glu Lys Val Leu Pro Ala Ala Lys Leu Ile Lys Arg Arg Asn Leu
                                -35
ttt tcc aca tgc act cct caa tat ggy aca cat gct gct ttc ttg tca
                                                                       150
Phe Ser Thr Cys Thr Pro Gln Tyr Gly Thr His Ala Ala Phe Leu Ser
        -25
                            -20
tta cat gcc tca ctt gtc acc aaa gca ttt tca atc aat tcc tgg gag
                                                                       198
Leu His Ala Ser Leu Val Thr Lys Ala Phe Ser Ile Asn Ser Trp Glu
tgg
                                                                      201
Trp
<210> 322
<211> 159
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<212> DNA
<213> Homo sapiens
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<221> CDS
<222> 77..157
<221> sig peptide
<222> 77..151
<223> Von Heijne matrix
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      seq PLLLCPLSSGSPC/PR
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                                                                        60
tggaagtggg ctgggg atg gtg tcg ggg gcc caa gct ccc agc tcc caa agg
                                                                       112
                  Met Val Ser Gly Ala Gln Ala Pro Ser Ser Gln Arg
                  -25
                                       -20
ccc ctg ctt cta tgc cct ttg agc tca ggt agc ccc tgc ccc cgg gg
                                                                       159
Pro Leu Leu Cys Pro Leu Ser Ser Gly Ser Pro Cys Pro Arg
                                 - 5
<210> 323
<211> 420
<212> DNA
<213> Homo sapiens
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<221> CDS
<222> 325..420
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<222> 325..405
<223> Von Heijne matrix
      score 5.5
      seq SFLPSLLSSFLLS/LP
<221> misc_feature
<222> 117
<223> n=a, g, c or t
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                                                                       60
gcctttttga ttttgcatgt gtataatctg gctctgaaat cagtgacacg aagtganctt
                                                                      120
cgaaacaagc ctgagcaata gaagtagatg tggaaataac ttcggtttct caaggcaaat
                                                                      180
actttgatag gaacaaacaa ccgtttagat atagaagatg tgatacattc ctttaaaaag
                                                                      240
aatttgacct tatgtcattg taggcacacc tcatatttca attattcata tagtttttct
                                                                      300
tgagcaattg ctggtttaag aata atg tca tgt ctt ttg cgt gct tat atc
                                                                      351
                           Met Ser Cys Leu Leu Arg Ala Tyr Ile
                                   -25
att tgg ata ttt cct tcc ttc ctt cct tcc ctc ctt tct tcc ttc ctt
                                                                      399
Ile Trp Ile Phe Pro Ser Phe Leu Pro Ser Leu Leu Ser Ser Phe Leu
            -15
                                -10
                                                     -5
ctt tcc ctc ccc cct tcc ggg
                                                                      420
Leu Ser Leu Pro Pro Ser Gly
        1
<210> 324
<211> 210
<212> DNA
<213> Homo sapiens
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<221> CDS

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 <222> 9..209
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 <222> 9..116
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    seq LHFVYCFLCCAEA/FL
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                                                                        50
         Met Phe Gln Leu Leu Ile Leu Cys Gln Met Asn Ser Leu Lys
              -35
                                  -30
 ata ttt tct ccc att ctt gga tgg tct ctt cat ttt gtt tat tgt ttc
                                                                        98
 Ile Phe Ser Pro Ile Leu Gly Trp Ser Leu His Phe Val Tyr Cys Phe
                             -15
 ctt tgc tgt gca gaa gcc ttt tta ctt gat atg atc cca ttt atg caa
                                                                       146
 Leu Cys Cys Ala Glu Ala Phe Leu Leu Asp Met Ile Pro Phe Met Gln
                                         5
                                                              10.
 ttt tac ttt ggt tac ctg tgc ttg tgg ggt att act tta aaa atc ttt
                                                                       194
Phe Tyr Phe Gly Tyr Leu Cys Leu Trp Gly Ile Thr Leu Lys Ile Phe
                                     20
gcc cag tcc aat tgg g
                                                                       210
Ala Gln Ser Asn Trp
             30
<210> 325
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<222> 31..192
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<222> 31..174
<223> Von Heijne matrix
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      seq VCLRLHVLSAVQT/ER
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                                 Met Ala Leu Leu Gly Lys Arg Cys
gac gtc ccc acm aac ggc tgc gga ccc gac cgc wgg aam wac ggc gwy
                                                                      102
Asp Val Pro Thr Asn Gly Cys Gly Pro Asp Arg Xaa Xaa Xaa Gly Xaa
-40
                    -35
                                        -30
aac eeg caa ara ega gat cat cae cag emt mgt gte tge ett aga ete
                                                                      150
Asn Pro Gln Xaa Arg Asp His His Gln Xaa Xaa Val Cys Leu Arg Leu
                -20
                                    -15
cat gtg ctc agc gct gtc car act gaa cgc cga ggt gat ggg
                                                                      192
His Val Leu Ser Ala Val Gln Thr Glu Arg Arg Gly Asp Gly
                                1
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<211> 181
<212> DNA
<213> Homo sapiens
<220>
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                                                                        60
agegegtegt atg egg eea gea eta agg tee tte tgg eac tee tet ggt
                                                                       109
           Met Arg Pro Ala Leu Arg Ser Phe Trp His Ser Ser Gly
                   -30
                                        -25
                                                            -20
gga ccg ccc cca tcg gcc aca ctt gcc ctg ctc tcc agt gat tct gta
                                                                      157
Gly Pro Pro Pro Ser Ala Thr Leu Ala Leu Leu Ser Ser Asp Ser Val
                -15
                                     -10
get act qge tee gta gte teg eqq
                                                                      181
Ala Thr Gly Ser Val Val Ser Arg
            1
<210> 327
<211> 185
<212> DNA
<213> Homo sapiens
<220>
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<222> 39..185
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<223> Von Heijne matrix
      score 5.5
      seq LFSGWLVWWGSRS/SQ
<221> misc feature
<222> 143,145,175
<223> n=a, g, c or t
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                                                                       56
                                          Met Leu Cys Ala Cys Lys
gca cgt ggg gtg atg ctg ctg ttc tca ggg tgg ttg gtt tgg tgg
                                                                      104
Ala Arg Gly Val Met Leu Leu Phe Ser Gly Trp Leu Val Trp Trp
-20
                    -15
                                        -10
ggc agt agg tcc tca cag two ctc aga atg cct gag agn tna qta aqt
                                                                      152
Gly Ser Arg Ser Ser Gln Xaa Leu Arg Met Pro Glu Xaa Xaa Val Ser
ggg gag ggt cga agc gat cdv dng cca cat ggg
                                                                      185
Gly Glu Gly Arg Ser Asp Xaa Xaa Pro His Gly
        15
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<400> 332

183

<222> 135..203 <223> Von Heijne matrix score 5.5 seg LPFVCLLLRNVYS/DL <400> 330 aacaqtqtqt gagagttccc tttcctccac atcctcqcca qcatctqtta ttqcctqtct 60 ttttgatacg agccttttta acaggggtaa gatgatatct cattgtagtt ttgatttqca 120 ttctctgatg atca atg atg ttg agc acc ttt tca tat gcc tgt ttg cca 170 Met Met Leu Ser Thr Phe Ser Tyr Ala Cys Leu Pro -20 ttt gta tgt ctt ctt ttg aga aat gtc tat tca gat ctt ttg ccc aat 218 Phe Val Cys Leu Leu Leu Arg Asn Val Tyr Ser Asp Leu Leu Pro Asn -10 223 cgg gg Arg <210'> 331 <211> 362 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 272..361 <221> sig\_peptide <222> 272..343 <223> Von Heijne matrix score 5.5 seq LIVVLVCISLVII/DD <400> 331 aatggacacc taggttgctt ccatatctga gctattgtga ataatgctgc aatgaacatg 60 ggagtggaga catctcctaa gcatactgat ttcagttcct ttgggtatat acccagaagt 120 gggatcatgt ggtaatcttg tttttacttt tttgaggaac ctccatacca ttatccatga 180 tggctatagt aatttacatt cataccagca gtgcacaagg gtctcctttt ctgtatacac 240 ttgccaacac ttgttatctt tcattttttt g atg cta gcc att cta aca ggt 292 Met Leu Ala Ile Leu Thr Gly ggg agg tgg tat ctc ata gtg gtt tta gtt tgc att tcc ttg gtg att 340 Gly Arg Trp Tyr Leu Ile Val Val Leu Val Cys Ile Ser Leu Val Ile -15 -10 att gat gat gag cac ggg g 362 Ile Asp Asp Glu His Gly <210> 332 <211> 89 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 34..87 <221> sig\_peptide <222> 34..75 <223> Von Heijne matrix score 5.5 seq LLPLGLKVLGLQA/RG

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aaa gtg ctg gga tta cag gcg aga ggc acc acg ct Lys Val Leu Gly Leu Gln Ala Arg Gly Thr Thr -5	85
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catcetegte getgeagega cacaegetet egeegeegee atgaetgage tegtgggeace etcaagggee acaaeggetg ggtaacecag ategetacta eceeggacatg atceteteg cetetegagg taeggaetaa gataagaeca gaaactgaee aggg atg aga cea act atg gaa tte cac age gtg  Met Arg Pro Thr Met Glu Phe His Ser Val	agatgaccct 120 ccccgcagtt 180 tcatcatgtg 240
-25 -20 ggg gtc act ccc act ttg tta gtg atg tgg tta tct cct cag Gly Val Thr Pro Thr Leu Leu Val Met Trp Leu Ser Pro Gln -15 -10 -5	ata aaa
agt tcg ccc tct cag gct cct ggg atg gaa ccc tgc gcc tct Ser Ser Pro Ser Gln Ala Pro Gly Met Glu Pro Cys Ala Ser 1 5 10	ggg atc 386 Gly Ile
tca caa cgg gca a Ser Gln Arg Ala 20	399
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<pre>2221&gt; sig_peptide 2222&gt; 33131 2223&gt; Von Heijne matrix     score 5.5     seq SLCLLTVAVLVLT/FK</pre>	÷
400> 334	
atgaagggt actagaacac ctgcccatcc at atg gga aaa aaa aaa a Met Gly Lys Lys Lys : -30	Ile Trp
cc cct agc tca tat ccc atg ccc agt cat aaa cat gta tcc of hr Pro Ser Ser Tyr Pro Met Pro Ser His Lys His Val Ser I -25 -20 -15	Leu Cys
tt cta acg gtt gca gtt tta gtt ctt aca ttt aag tct tta a	att cat 149

Leu Leu Thr Val Ala Val Leu Val Leu Thr Phe Lys Ser Leu Ile His -5 ttt gag tda att ttt gca tat gag ata ggg gtc cag ggg 188 Phe Glu Xaa Ile Phe Ala Tyr Glu Ile Gly Val Gln Gly 10 <210> 335 <211> 115 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 23..115 <221> sig\_peptide <222> 23..94 <223> Von Heijne matrix score 5.5 seq CPSLLSPISPSQA/CP <400> 335 ccaatacaca tcactcagtg gc atg agc cct gtc ctc tgc ttc cat cgc tgc 52 Met Ser Pro Val Leu Cys Phe His Arg Cys -20 tcc tgt ccc tcc ctc ctc agc ccc atc tcc cca tcc cag gcc tgt cct 100 Ser Cys Pro Ser Leu Leu Ser Pro Ile Ser Pro Ser Gln Ala Cys Pro -10 -5 gag ccc ctc ctt ggg 115 Glu Pro Leu Leu Gly <210> 336 <211> 300 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 197..298 <221> sig\_peptide <222> 197..268 <223> Von Heijne matrix score 5.5 seq IMFVCMCVCVCVC/VY <400> 336 catgcttgtt gtaacgtgtc aaacaataca gaggtgtagg gaaaatacct agtgccaccc 60 tccactccaa aaccccatgt cgccagagat aaccatttat tcagacagtg agtatctatt 120 aagtatctat tgctaggctt tggagatagc ataatgaaca aaatggatgt gctctctgcc 180 cttgtgattt ggacag atg ctt cag tta tct ttt tct gtg ttt ata ttg att 232 Met Leu Gln Leu Ser Phe Ser Val Phe Ile Leu Ile -20 atg ttt gta tgt atg tgc gtg tgt gtg tgt gtg tgt gtg tat cga ctg 280 Met Phe Val Cys Met Cys Val Cys Val Cys Val Cys Val Tyr Arg Leu -10 ttt tct tcc tcc tcc ccg gg 300 Phe Ser Ser Ser Pro

<210> 337 <211> 307

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      Met Lys Ser Thr Val Ser Ser Arg Glu Val Ala Thr Val Asp Lys
                                                                        49
                              -85
                                                   -80
 atg aaa aga cgc cat gca gaa tac tgt gca cag ggt ctc cag aga ttt
 Met Lys Arg Arg His Ala Glu Tyr Cys Ala Gln Gly Leu Gln Arg Phe
                                                                        97
                         -70
                                             -65
 aaa gcc caa ctt tct caa gat acc ctt ccc cav cat cca cat ctg gag
 Lys Ala Gln Leu Ser Gln Asp Thr Leu Pro Xaa His Pro His Leu Glu
                                                                       145
 -60
                     -55
                                         -50
 awa gag aag ggg ctt gaa ggc ttg gag gaa aat gtg cct cta aag gga
 Xaa Glu Lys Gly Leu Glu Glu Glu Asn Val Pro Leu Lys Gly
                                                                       193
                                     -35
 gag aaa cct gga gaa ggg ggt cca gag tct cct aag aag aga aga agg
                                                                       241
 Glu Lys Pro Gly Glu Gly Gly Pro Glu Ser Pro Lys Lys Arg Arg Arg
             -25
                                . -20
                                                     -15
gtg ctt ctc gga gcg ggc atc cca cca gta agc tca gct ccc agg aga
Val Leu Leu Gly Ala Gly Ile Pro Pro Val Ser Ser Ala Pro Arg Arg
                                                                       289
         -10
cag agc cag cag gca aca
                                                                       307
Gln Ser Gln Gln Ala Thr
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                                                                       51
                Met His Asn Ser Cys Arg Pro Val His Leu Phe Phe
                 -20
                                     -15
ttt ttt ttt yct gag aca ggt tct cgt tct aat ycc tgg ctg gag tsc
Phe Phe Phe Xaa Glu Thr Gly Ser Arg Ser Asn Xaa Trp Leu Glu Xaa
                                                                       99
agt ggt gcg atc ata gct aac tcc
                                                                      123
Ser Gly Ala Ile Ile Ala Asn Ser
   10
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 gettgaagga gecaacetea attgeagaga geageegtea eeceagetae egeteagage
                                                                        120
 ccagettgga accagagage tteegttete ctacetttgg caaaagtttt cacttegate
                                                                        180
 cactatccag tggctcacgc tcctccagcc tcaagtcagc ccagggcaca ggctttgagc
                                                                        240
 tgggccagtt gcaatccatt cgttcagagg gcaccacctc cacctcctaa taagagcctg
                                                                        300
 gccaaccagn nacgcaa atg gaa gcc tat ctt aat gac agc ttg ctc aca
                                                                        350
                    Met Glu Ala Tyr Leu Asn Asp Ser Leu Leu Thr
                                                 -35
 cet tea gae age eet gat tit gag tea gig eag gea ggg eet gna gee
                                                                       398
 Pro Ser Asp Ser Pro Asp Phe Glu Ser Val Gln Ala Gly Pro Xaa Ala
     -30
                         -25
                                              -20
 aga ccc acc ttt agg cta tac ctc tcc ctt cct gtc agc cag gct ggc
                                                                       446
 Arg Pro Thr Phe Arg Leu Tyr Leu Ser Leu Pro Val Ser Gln Ala Gly
 -15
                     -10
 cca gc
                                                                       451.
 Pro
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<222> 244..245
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gteteetgat ccageeggee etgecaggtg ace atg eet get etg gge eea get
                                                                       114.
                                      Met Pro Ala Leu Gly Pro Ala
                                                      -10
ctt ctc cag ggc tct ctg kgc cgv gtg ggt cct cac cct cca gcs cct
                                                                       162
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Leu Leu Gln Gly Ser Leu Xaa Arg Val Gly Pro His Pro Pro Ala Pro
 tee ace aac tge att cae tee caa tgg cae gta tet gea gea esk gge
                                                                       210
 Ser Thr Asn Cys Ile His Ser Gln Trp His Val Ser Ala Ala Xaa Gly
                     15
                                          20
                                                              25
 aag gga ccc cac ctc agg cac cct ctr sct ggg nns tac caa ctt cct
                                                                       258
 Lys Gly Pro His Leu Arg His Pro Leu Xaa Gly Xaa Tyr Gln Leu Pro
                 30
                                      35
 gtt cca gct gag ccc tgg gct gca gct gga ggc cac agt gtc cac c
                                                                       304
 Val Pro Ala Glu Pro Trp Ala Ala Ala Gly Gly His Ser Val His
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                                                                      120
aamcvacttt tcatcaggtt tttaacttaa gtcgtgagga atacaacggt gaacacaaga
                                                                      180
ttcattttat tttcatcacc atgggacgta tcctgttgtt gagttctctg ggtcagacct
                                                                      240
ctgaagactt ctcagatgga tcctagtctc wrrgcttgcc ctgaaattac tcgctgctca
                                                                      300
gggagagagt tgaa atg gtt ggc atc ctc cca ctc tgt tgc tcc ggc tgt
                                                                      350
                Met Val Gly Ile Leu Pro Leu Cys Cys Ser Gly Cys.
                                 -15
gtc ccc tcg ctc tgt tgt tcc agc tat gt
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Val Pro Ser Leu Cys Cys Ser Ser Tyr
        -5
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agcgtgggcc aggacagcgg gaggtaagtc gccaagaaaa gggttgggaa ragctcagaa
                                                                      120
teggaegget aggaagaaat gaecaaaagg ageetgatag eeceetatte tgeaegetgt
                                                                      180
teetggaaac egeetttgea aagacagtga gagaaateta ac atg get cac tee
                                                                      234
                                               Met Ala His Ser
ate ttg ett eta gee teg eag gee gge tgt ett ege tea tte etg gge
                                                                      282
Ile Leu Leu Ala Ser Gln Ala Gly Cys Leu Arg Ser Phe Leu Gly
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WO 99/53051 189 -10 - 5 1 5 aat tgg g 289 Asn Trp <210> 343 <211> 169 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 78..167 <221> sig\_peptide <222> 78..137 <223> Von Heijne matrix score 5.40000009536743 seq WVFLVAIFKGVHC/EG <400> 343 agetetggga gaggageece egecetggga tteccaggtg ttttcatttg gtgateagea 60 ctgaacacag aagagtc atg acg gag ttt ggg ctg agc tgg gtt ttc ctt 110 Met Thr Glu Phe Gly Leu Ser Trp Val Phe Leu -20 -15 gtt gct att ttt aaa ggt gtc cac tgt gaa ggt cma att ggt gga gtc 158 Val Ala Ile Phe Lys Gly Val His Cys Glu Gly Xaa Ile Gly Gly Val ggg ggg gcg gg 169 Gly Gly Ala 10 <210> 344 <211> 112 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 63..110 <221> sig\_peptide <222> 63..104 <223> Von Heijne matrix score 5.40000009536743 seq NTVFLLLFFGCFF/FE <400> 344 tgtgttttct ctgtcccaaa ttaaatgcat tggggaagtt tataattaca ggaattccac 60 107 Met Asn Thr Val Phe Leu Leu Leu Phe Phe Gly Cys Phe Phe gag ac 112 Glu <210> 345 <211> 349 <212> DNA <213> Homo sapiens

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gattcatcc	cacg:	ctaaac	actca	ittct	a cc	caac	tgat	taa	gaca	gaa	caga	agata	aa 12
ctgaaactt	c tetg	ccttcc	cgctc	gcaag	a aq	tqaa	tgag	cga	tece	tct	caac	taact	k 18
raa atg t	tt gcc	tca c	cc ago	j aga	tgg	agc	tct	nca	aao	acc	tto	tct	1 22
Met P	he Ala	Ser P	ro Arg	J Arg	Trp	Ser	Ser	Xaa	Lys	Ala	a Phe	Ser	1.
		-30				-25					-20		
ggc cag c	gg aca	ctc c	ta tct	gcc	atc	ctc	agc	atg	cta	tca	cto	agc	270
Gly Gln A	rg inr	Leu L	eu Ser	Ala		Leu	Ser	Met	Leu	Ser	Let	Ser	
***	,-15				-10					-5			
ttc tcc a	Ca aca	Com I	ra cro	agc	aac	tac	tgg	ttt	gtg	ggc	: aca	cag	324
Phe Ser T	111 1111	ser n	eu res	Ser	Asn	Tyr	Trp		Val	Gly	Thr	Gln	
_		CCC C	o ta taa					10					
aag gtg c Lys Val P	ro Lvs	Pro L	eu Cve	gag	two	ggt	ctg	gca	gcc	aag	tgo	ttt	372
15	10 2,0	20	n N	Giu	пур	GIY		Ата	Ala	ьуs	Cys		
gac atg c	ca qtq			gga	ast	200	25	202				30	
Asp Met P	ro Val	Ser Le	eu Asp	Glv	Asn	Thr	aac λen	Thr	C00	acc mb-	Cag	gag	420
		35	p	Q- <i>j</i>	пор	40	Mali	1111	ser	Inr	45	GIU	
gtg gta m	ma ta					- 0					43		1 423
Val Val Xa		•		•									,' 431
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	e 5.40			3					,				
seq	HSVFLC	APALVE	P/RP									٠.	
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cacggttcag	, attcg	gtacc a	agaggo	:gtag	ggg	cggc	cgq .	acta	atac	aa c	taac	iggaco	T 180
cctcaccccc	ctgga	g atg	ccc at	a ca	t tc	c gt	a tt	c ct	c tg	it go	cc cc	c qc	232
		Met :	Pro Il	e Hi	s Se	r Va	l Ph	e Le	u Cy	s Al	la Pr	o Ala	a
			-15				-1	0				-5	
tc gtc tt	e Pro	egg cc	g gtg	gcc	tgg	aag	gcg	gag	agg	ccc	agc	ttg	280
Leu Val Ph	E PIO	arg Pro	o vai			гуs	Ala	Glu	Arg		Ser	Leu	
ac ttt aa	t acc t	ca at			5					10			
gc ttt gg	v Ala o	er Lei	. Pro	DYO 1	CEC	999	cgt	tct	cta	ctg	999	cag	328
Cys Phe Gl	,	OT DC	4 F10	20	beu '	GIY .	arg :			Leu	GIY	GIn	
gg agc ag		att to	taa		202	~~~	aat .		25				
Sly Ser Se	r Phe 1	ile Sei	r Trn	Glv '	rh-	-1-	act o	gca .	all 	gta	gag	tta -	376
30			35	Oly .	1111	2111		40	шe	vaı	GIU	Leu	
aa cct ca	t t						•	• 0					200
aa Pro Hi													386
5	_						•						20
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193

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                                                                         60
 aattcaa atg gta tac gat gaa aaa tot oto too tgt too cat acc oca
                                                                        109
         Met Val Tyr Asp Glu Lys Ser Leu Ser Cys Ser His Thr Pro
                 -60
                                      -55
 gee ace cag tte ete tee tgg gat gea tee agt gtt tae agt tte tta
                                                                        157
Ala Thr Gln Phe Leu Ser Trp Asp Ala Ser Ser Val Tyr Ser Phe Leu
             -45
                                 -40
 tat atc ctc tca gca aga gtt aat gta gac gta dgc agm tac att cgt
                                                                        205
Tyr Ile Leu Ser Ala Arg Val Asn Val Asp Val Xaa Xaa Tyr Ile Arg
         -30
                             -25
                                                  -20
gtg tac ata ctt gcc tgt gtg ttt ttc ctc tca cac ccc ctt ttt aad
                                                                        253
Val Tyr Ile Leu Ala Cys Val Phe Phe Leu Ser His Pro Leu Phe Xaa
                         -10
sra cca aat ggt agt gta tat tgt cnm cgt cat tct ccc cct tac ctt
                                                                        301
Xaa Pro Asn Gly Ser Val Tyr Cys Xaa Arg His Ser Pro Pro Tyr Leu
                                     10
ttt tgc
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Phe Cys
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                                                                        58
ctg cct tta tca cct act aaa ttc cta aat gtg ttc ttg ggc ctg ttc
                                                                       106
Leu Pro Leu Ser Pro Thr Lys Phe Leu Asn Val Phe Leu Gly Leu Phe
-35
                    -30
                                         -25
ctc tat tat ctt caa ttg gta tgt ctg ctt att att tct ttg gtt ttg
                                                                       154
Leu Tyr Tyr Leu Gln Leu Val Cys Leu Leu Ile Ile Ser Leu Val Leu
                -15
                                     -10
ata tct ggg tta ggg g
                                                                       170
Ile Ser Gly Leu Gly
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   <222> 149..235
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         seq LNQTLMLLREVLA/SH
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   ctgcattatt gactaccatt gaagaaatgc atttgctaag caaaaaaata ttcttcaatt
                                                                         120
   agcttgaagt cttcatgcaa gtaaatta atg gac aag gtt gaa ctc cca cca
                                                                         172
                                  Met Asp Lys Val Glu Leu Pro Pro
  ect gat ett gga eca agt tet gea eta aat eag aca ete atg ttg etg
                                                                         220
  Pro Asp Leu Gly Pro Ser Ser Ala Leu Asn Gln Thr Leu Met Leu Leu
      -20
                           -15
                                               -10
  cgt gaa gtt tta gca tct cac gat tct tca gtk gta cca tta gat gct
                                                                         268
  Arg Glu Val Leu Ala Ser His Asp Ser Ser Val Val Pro Leu Asp Ala
                                       5
  cgt caa gct gat ttt gtg cag ggg g
                                                                         293
  Arg Gln Ala Asp Phe Val Gln Gly
              15
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                                                                        120
  ttgnraggcc caaggagagg gagagag atg ggg gga aca gct ggt tgg agc agt
                                Met Gly Gly Thr Ala Gly Trp Ser Ser
                                        -30
  cag aac aca cac aac att kga gta cac cat ctt gtg tgg ctg tgg ttc
                                                                        222
 Gln Asn Thr His Asn Ile Xaa Val His His Leu Val Trp Leu Trp Phe
              -20
                                  -15
                                                       -10
  gtg gtc ccc caa aca att aca atg ata aca cca aag atc act gaa cac
                                                                        270
 Val Val Pro Gln Thr Ile Thr Met Ile Thr Pro Lys Ile Thr Glu His
          - 5
 aga cca sta ata aca gat atr dtr ata atg aya aca ttt gaa awa ttg
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ctg att gca cgg gtg tac ttt tgt att tat gtg tgt gtg tgg tt Leu Ile Ala Arg Val Tyr Phe Cys Ile Tyr Val Cys Val Trp 1 5 10	93
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tta ttt cct gtt ctt tgg atg ttt cta gtg tat ttc ttt ctt tct Leu Phe Pro Val Leu Trp Met Phe Leu Val Tyr Phe Phe Leu Ser Ser -5	160
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                                                                    102
Cys Val Tyr Leu Phe Cys Ala Cys Met Cys Val Cys Ala Phe Phe
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                               - 5
ttt tt
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Phe
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                                                                    55
                                               Met Lys Xaa Asn
                                                   -35
aac ctc cgg cga cag agc ccc gct ctc agg cac tgc tgg aga mcc gag
                                                                   103
Asn Leu Arg Arg Gln Ser Pro Ala Leu Arg His Cys Trp Arg Xaa Glu
        -30
                           -25
                                               -20
acc gac ttc ttt ctc ttt acc ctc att ggc gct tct ctc ctg cag tcc
                                                                   151
Thr Asp Phe Phe Leu Phe Thr Leu Ile Gly Ala Ser Leu Leu Gln Ser
                       -10
gcc tct ggg ccc tgc cgc att tct tsa smc tta aag tgg cat tct aaa
                                                                   199
Ala Ser Gly Pro Cys Arg Ile Ser Xaa Xaa Leu Lys Trp His Ser Lys
ggc act tta a
                                                                   209
Gly Thr Leu
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3 92

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Ser Leu Gly Val Gly Pro Ala Gly Pro Lys Xaa Gly Val Ile Ser Gln

ttg gag cga ggg gat gag ccc tgg gtc ctg gat gtt cag ggc acc tct

WO 99/53051 PCT/IB99/00712

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 ggg aaa gag cac ctg aag aag tca aca gcc cag ctc ttg gga cca gaa
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Gly Lys Glu His Leu Lys Lys Ser Thr Ala Gln Leu Leu Gly Pro Glu
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                                 80
 ctg aag tac aag gag ttg ay
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                                                                       120
acggtggagt tgcaggatca gcttgaagaa ct atg atc ccc aga agg aca agc
                                                                       173
                                     Met Ile Pro Arg Arg Thr Ser
get tet egg gea eeg tea gte eee caa aac gea gge tta agt eea ete
                                                                       221
Ala Ser Arg Ala Pro Ser Val Pro Gln Asn Ala Gly Leu Ser Pro Leu
                    -25
                                         -20
ccc gcc cta agt tct ctg tgt gtg tcc tgg ggg acc agc agc act gtg
                                                                       269
Pro Ala Leu Ser Ser Leu Cys Val Ser Trp Gly Thr Ser Ser Thr Val
                -10
                                     -5
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60

199

199													
aatactttca cagtttttca tagcagaaat ttataaatta atgaagccca ctttatactt ttatttcttt t atg gtt tgc atc ttt tgt ttc tta act tcg aaa gct ttt  Met Val Cys Ile Phe Cys Phe Leu Thr Ser Lys Ala Phe  -10	180 230												
Cct aac cct aga tca cag gat ttt ctc tta gat ttc tct agg cat tnt Pro Asn Pro Arg Ser Gln Asp Phe Leu Leu Asp Phe Ser Arg His Xaa  1 5 10 15	278												
ata ggt tta ggt ttc aca ttt agg tcc gca atg cat ttt gaa aac ttc Ile Gly Leu Gly Phe Thr Phe Arg Ser Ala Met His Phe Glu Asn Phe 20 25 30	326												
cgt ctg waa ggt ttg ggt caa gat tcc ctt tgt c Arg Leu Xaa Gly Leu Gly Gln Asp Ser Leu Cys 35 40	360												
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-20 -15 -10 gtc aca agc agt cct ctt gcc tca gca ggt agg act aca cgc Val Thr Ser Ser Pro Leu Ala Ser Ala Gly Arg Thr Thr Arg -5 1 5	212												
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tcactk atg tca ctg twt ahg cta tgt gac cct gac cta gtt cct tgc	168
Met Ser Leu Xaa Xaa Leu Cys Asp Pro Asp Leu Val Pro Cys	, 100
- · · · · · · · · · · · · · · · · · · ·	•
10	
cct ctc ttg atc tca gtt gct tta tct gta aaa ttt cac att tkt cag	216
Pro Leu Leu Ile Ser Val Ala Leu Ser Val Lys Phe His Ile Xaa Gln	
-5 1 5	
caa gtc aac ctt cca tgt tcc tct ca	242
Gln Val Asn Leu Pro Cys Ser Ser	
10 15	
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aaa aga aac ccc aaa cct gtt aca gtc cct gct ttt ctg csc cct tgc	96
Lys Arg Asn Pro Lys Pro Val Thr Val Pro Ala Phe Leu Xaa Pro Cys	90
-25 -20 -15 -10	
ttg act tet tte tet tgt ket gga gea tet tte tet etk ttw ggt gdg	144
Leu Thr Ser Phe Ser Cys Xaa Gly Ala Ser Phe Ser Leu Xaa Gly Xaa	
-5 1 5	
aga agg ggt tgg caa cat ggc agc tgc tgc tcc acc att ccc tta ttt	192
Arg Arg Gly Trp Gln His Gly Ser Cys Cys Ser Thr Ile Pro Leu Phe	
10 15 20	
csa act cta aat tcc ctt ggg cag gga ctc att ggc cca gcc tac ata	240
The Tou Ace See Lou Cly Cly Cly Lou Tla Cly Dra Sla Mar The	240
Xaa Thr Leu Asn Ser Leu Gly Gln Gly Leu Ile Gly Pro Ala Tyr Ile	
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tcg	gcc	gst	gtt	ctg	wcg	cct	tgo	tgo	tgt	cac	gcg	ggc	gct	tcg	tcc		97
-20					-15					-10					Ser -5		
Gly	Ala	Thr	Ala	Trp 1	Glu	Glu	Thr	Pro 5	Arg	Ser	Arg	Cys	His	Ile	gcc Ala		145
Val	Xaa	Ser	Thr	Asn	Thr	Ala	Ser 20	Arg	Gly	Arg	Thr	Trp 25	Cys	Arg	gcg Ala		193
acg Thr	gga Gly 30	ccg Pro	tgc Cys	cct Pro	tct Ser	999 Gly 35	ccc	acg Thr	cgg Arg	gga Gly	gta Val 40	agc Ser	cgg Arg	agc Ser	aga Arg	,	241
999 Gly 45	.ctg Leu	ggg ggg	gcc Ala	ggg Gly	ttc Phe 50	ctc Leu	tcc Ser	ccc Pro	ttc Phe	tgc Cys 55	tgc Cys	ct c Leu	ttc Phe	gcc Ala	ttt Phe 60		289
cat His	ccg Pro	cgg Arg	cta Leu	ccc Pro 65	tgg Trp	tgt Cys	gct Ala	gag Glu	gtt Val 70	ccc Pro	gtt Val	cca Pro	gca Ala	gct Ala 75	qca		337
cac His	cat His	atg Met	cgc Arg 80	tgt Cys	gga Gly	ggg Gly	Asp	ctc Leu 85	ctg Leu	gca Ala	gcc Ala	Pro	ccg Pro 90	ccg Pro	ggt Gly		385
Pro	Ser	Trp 95	Phe	Ala	cgg Arg	ttc Phe	cct Pro 100	ccg Pro	ctt Leu	gtc Val	ccc Pro	gag Glu 105	tct Ser	ttc Phe	cct Pro		433
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	> 36																
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ggt Gly	ctt Leu	att Ile	Trp	gtc Val -10	ttt Phe	ggt Gly	ctt Leu	gta Val	tct Ser -5	gtt	ttg Leu	agt Ser	bga Xaa	ttt Phe 1	ttq		99
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ctg tcc ctt gtc tct aat tgt aac ttt gta ctc act gac caa ctt ttc
                                                                       104
Leu Ser Leu Val Ser Asn Cys Asn Phe Val Leu Thr Asp Gln Leu Phe
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cct gcc cct gcs tcc ctc atc ccc gaa g
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Pro Ala Pro Ala Ser Leu Ile Pro Glu
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                                         -20
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Lys Thr Gly Val Phe Leu Phe Ser Ile Ile Gly Ser Phe Gly Phe Pro
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                                     -5
gga atg tgc aat tgt aaa aac cca gcc cgg g
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-15

tgg agt tcc cag gtt ccc agc tcc ccc cct gca agc ctt gaa gcc tcc

-10

100

									2.0	_						•	
Trp	Ser	Ser -5	Gln	Val	Pro	Ser	Ser 1	Pro	Pro	Ala	Ser 5	Leu	Glu	Ala	Ser		
agc Ser 10	aac Asn	gtc Val	tat Tyr	ctc Leu	cag Gln 15	gag Glu	agc Ser	agg Arg	gca Ala	gcc Ala 20	tat Tyr	gca Ala	agt Ser	gtt Väl	ccg Pro 25		148
gca Ala	gga Gly	cca Pro	gaa Glu	gtg Val 30	gcc Ala	act Thr	caa Gln	cac His	acg Thr 35	tcc Ser	tca Ser	cca Pro	gtc Val	acc Thr 40	cct Pro		196
atg Met	g.	٠								4							200
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	> 37 accc		caca	gcac	t tạ	cctg	tttt	taa	tgaa	tct	aatt	atto	ac a		caa Gln		57
Leu	Leu	tat Tyr	tta Leu '	aca Thr	Tyr	Ser	tta Leu	gct Ala	ttc Phe	ctg Leu	Leu	ttt Phe	atc Ile	aag	gct		105
	-15 acc Thr	g				-10			-		-5						112
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gggaggette gaegtegrnr aggragmmge tgeegegtta gtteegaget tgaagteact
                                                                       180
aggaettete teaaaettgt gtgetgagga gaeteag atg ttg gee tea get eet
                                                                       235
                                          Met Leu Ala Ser Ala Pro
                                                  -.40
agg ctg aac tca gca gat cgg ccc atg aaa act tct gta ttg aga caa
                                                                       283
Arg Leu Asn Ser Ala Asp Arg Pro Met Lys Thr Ser Val Leu Arg Gln
    -35
                         -30
                                             -25
agg aag gga tot gto aga aag caa cac ttg tta tot tgg got tdg cag
                                                                       331
Arg Lys Gly Ser Val Arg Lys Gln His Leu Leu Ser Trp Ala Xaa Gln
                     -15
yaa ggh aga kga cag gta gtg gag atc ctg caa tct gaa aag cag act
                                                                       379
Xaa Gly Arg Xaa Gln Val Val Glu Ile Leu Gln Ser Glu Lys Gln Thr
daa rgt gac g
                                                                       389
Xaa Xaa Asp
<210> 378
<211> 143
<212> DNA
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<222> 2..115
<223> Von Heijne matrix
      score 5.19999980926514
      seg LHGSLDAVSQAQG/RP
<400> 378
a atg tac ccc cta ggc agg gga gag cag ggc cct gct gca ccc aag tcc
  Met Tyr Pro Leu Gly Arg Gly Glu Gln Gly Pro Ala Ala Pro Lys Ser
              -35
                                  - 30
tgg ttg ctc ctc ccc acc aca ctg gcc ctc cat gga agc ctt gat gca
                                                                       97
Trp Leu Leu Pro Thr Thr Leu Ala Leu His Gly Ser Leu Asp Ala
        -20
                            -15
gtg agc cag gcc caa gga cgc ccc ggc cac cct gac gca ccc ccc a
                                                                      143
Val Ser Gln Ala Gln Gly Arg Pro Gly His Pro Asp Ala Pro Pro
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<221> CDS

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<210> 379
 <211> 261
 <212> DNA
 <213> Homo sapiens
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 <222> 198..260
 <221> sig_peptide
 <222> 198..245
 <223> Von Heijne matrix
       score 5.19999980926514
       seq FIAALFTIAETWN/QP
 <400> 379
 caqatqqtgg tgaggttgta gagaaaaagg aacgcttata cactqttqqt qcqaqtqtaa
                                                                         60
 attagtitaa ccattgigga agatgatatg gcaattccac aaagacctaa agicagraat
                                                                        120
 tmcmattcaa cccagtaatc ccattactgg gtatatactc aaaggaatat aaattqttqt
                                                                        180
 gttacaaaga cacatgc atg cgt gtg ttc att gca gca ctg ttc aca ata ,
                                                                        230
                    Met Arg Val Phe Ile Ala Ala Leu Phe Thr Ile
                        -15
 gca gag aca tgg aat caa ccc aaa tgc cca g
                                                                        261
 Ala Glu Thr Trp Asn Gln Pro Lys Cys Pro
 <210> 380
 <211> 228
 <212> DNA
 <213> Homo sapiens
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 <221> CDS
 <222> 63..227
<221> sig peptide
 <222> 63..152
 <223> Von Heijne matrix
       score 5.19999980926514
       seq LCFLSVHFRLRWG/DS
 <400> 380
 gggacgtggg aaaatgacta cgcgtcactc gtgatgtcgc gcatccgata ggcccttttc
                                                                         60
 ag atg gca aaa ggc ctg agg gtg aat ctg ggc gag ctg gtt gag tcc
                                                                        107
   Met Ala Lys Gly Leu Arg Val Asn Leu Gly Glu Leu Val Glu Ser
                                            -20
                        -25
 atg cgt ttg tgc ttc ctc tca gtc cac ttt cgc tta cga tgg ggc gac
                                                                        155
Met Arg Leu Cys Phe Leu Ser Val His Phe Arg Leu Arg Trp Gly Asp
                     -10
 -15
                                         -5
 tet tgt cca teg tea eet cae egg gaa aet ttt eet gee ggg eea gtt
                                                                        203
Ser Cys Pro Ser Ser Pro His Arg Glu Thr Phe Pro Ala Gly Pro Val
                                 10
 aat ggt ccc ctg tac cac ccc cgg g
                                                                        228
 Asn Gly Pro Leu Tyr His Pro Arg
         20
 <210> 381
 <211> 300
 <212> DNA
 <213> Homo sapiens
 <220>
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208
 <222> 39..299
 <221> sig_peptide
 <222> 39..89
 <223> Von Heijne matrix
    score 5.09999990463257
       seq QLLVLFGSQTGTA/OD
 <400> 381
 agtttttagt ctcagaccag accaccgggc gcgccccg atg ccg agc ccg cag ctt
                                                                        56
                                            Met Pro Ser Pro Gln Leu
 ctg gtg ctc ttc ggc agc cag aca ggc acg gct cag gat gtg tcg gag
                                                                       104
 Leu Val Leu Phe Gly Ser Gln Thr Gly Thr Ala Gln Asp Val Ser Glu
     -10
                         -5
 aga ctg ggt cgc gag gcc cgg ggc cgg ctt ggc tgc cgg gtg cag
 Arg Leu Gly Arg Glu Ala Arg Gly Arg Arg Leu Gly Cys Arg Val Gln
                 10
 gcc ctg gac tcc tac ccg gtg gtg aat ctg att aac gag ccc ctg gtg
                                                                       200
Ala Leu Asp Ser Tyr Pro Val Val Asn Leu Ile Asn Glu Pro Leu Val
                                 30
 ata ttt gtt tgt gca act ayw ggc caa gga gac ccc cct gac aac atg
                                                                       248
 Ile Phe Val Cys Ala Thr Xaa Gly Gln Gly Asp Pro Pro Asp Asn Met
                             45
aag aac ttc tgg agg ttt ata ttc cgg aag aac ctg ccc tcc acc gcc
                                                                       296
Lys Asn Phe Trp Arg Phe Ile Phe Arg Lys Asn Leu Pro Ser Thr Ala
cgg g
                                                                       300
Arg
70
<210> 382
<211> 151
<212> DNA
<213> Homo sapiens
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<221> CDS
<222> 8..151
<221> sig_peptide
<222> 8..130
<223> Von Heijne matrix
      score 5.09999990463257
      seq SFLFLACIFQGXS/XX
atacata atg tct tcc att ttg ggt gtc tca tcc tca tgg tgg tat tta
                                                                       49
        Met Ser Ser Ile Leu Gly Val Ser Ser Ser Trp Trp Tyr Leu
                                -35
                                                     -30
tat tat ggc tat tgt ata ttt gtt aaa aag tgc tct ttt tgc agt ttc
                                                                       97
Tyr Tyr Gly Tyr Cys Ile Phe Val Lys Lys Cys Ser Phe Cys Ser Phe
        -25
                            -20
ctg ttc ctt gcc tgt att ttt caa ggc tkt tck ckt kat wca aac aca
                                                                      145
Leu Phe Leu Ala Cys Ile Phe Gln Gly Xaa Ser Xaa Xaa Xaa Asn Thr
caa agc
                                                                      151
Gln Ser
<210> 383
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<211> 255

<212> DNA

<213> Homo sapiens

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<220>
<221> CDS
<222> 101..253
<221> sig_peptide
<222> 101..184
<223> Von Heijne matrix
      score 5.09999990463257
      seq CLCGSAPCLLCRC/CP
<400> 383
gcgtccggaa gtgtctcgca gatagtaaat aatctcggaa aggcgagaaa gaagctgtct
                                                                       60
ccatcttgtc tgtatccgct gcwcttgtga cgttgtggag atg ggg agc gtc ctg
                                                                       115
                                             Met Gly Ser Val Leu
ggg ctg tgc tcc atg gcg agc tgg ata cca tgt ttg tgt gga agt gcc
                                                                       163
Gly Leu Cys Ser Met Ala Ser Trp Ile Pro Cys Leu Cys Gly Ser Ala
            -20 -
                                 -15
ccg tgt ttg cta tgc cga tgc tgt cct agt gga aac aac tcc act gta
                                                                       211
Pro Cys Leu Leu Cys Arg Cys Cys Pro Ser Gly Asn Asn Ser Thr Val
act aga ttg atc tat gca ctt ttc ttg ctt gtt gga gta tgg gg
                                                                       255
Thr Arg Leu Ile Tyr Ala Leu Phe Leu Leu Val Gly Val Trp
<210> 384
<211> 456
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 128..454
<221> sig_peptide
<222> 128..265
<223> Von Heijne matrix
      score 5.09999990463257
      seq IGSCSVMSSGALC/VP
<400> 384
tacaactttg aaaagccctt cctctggctt gctagacagc tcattggaga ccgtaacttg
                                                                       60
gaatttgttg ccatgcctgc tettgcctca ccagagattg tcatggaccc aaatttggca
                                                                      120
gtgtagt atg agc wkr wtt agm agg ttg stt aga caa ctg ctc tcc cag
                                                                      169
        Met Ser Xaa Xaa Xaa Arg Leu Xaa Arg Gln Leu Leu Ser Gln
            -45
                                -40
rtg agg rwg atg acc tgt gag aat gaa gct gga gcc cag tgt car aag
                                                                      217
Xaa Arg Xaa Met Thr Cys Glu Asn Glu Ala Gly Ala Gln Cys Gln Lys
                            -25
                                                 -20
tot agt tit ata ggc agc tgt tot gtg atg toa agt ggt gca otg tgt
                                                                      265
Ser Ser Phe Ile Gly Ser Cys Ser Val Met Ser Ser Gly Ala Leu Cys
    -15
                        -10
gtg cca ctt tat tat cta gct aag ggc aac atg tgc tcc atc tgt ggg
                                                                      313
Val Pro Leu Tyr Tyr Leu Ala Lys Gly Asn Met Cys Ser Ile Cys Gly
                                    10
atg ctg aag gag atg aat ggg ctt tgg agt gaa tgt gac agt tta aaa
                                                                      361
Met Leu Lys Glu Met Asn Gly Leu Trp Ser Glu Cys Asp Ser Leu Lys
           20
                                25
aat acc ttc att gtt tgg rcc tgc ata ttt agc tgt ttg gga atg caa
                                                                      409
Asn Thr Phe Ile Val Trp Xaa Cys Ile Phe Ser Cys Leu Gly Met Gln
                            40
ttg awt tct tct kgr gtt tca aat gta aga ctg cta ctg tca cat ca
                                                                      456
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Leu Xaa Ser Ser Xaa Val Ser Asn Val Arg Leu Leu Ser His
 <210> 385
 <211> 193
 <212> DNA
 <213> Homo sapiens
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<221> CDS
 <222> 1..192
<221> sig_peptide
<222> 1..78
<223> Von Heijne matrix
      score 5.09999990463257
      seq AFPFVCLTFCVGG/GP
<400> 385
atg cct cat cca ctg gct acc tct gcg ttt ctg cgt tcc gcc ttt cct
                                                                        48
Met Pro His Pro Leu Ala Thr Ser Ala Phe Leu Arg Ser Ala Phe Pro
                         -20
                                             -15
ttt gtt tgt ctc acg ttt tgc gtg gga ggc ggt ccc ggg att tca ggg
                                                                        96
Phe Val Cys Leu Thr Phe Cys Val Gly Gly Gly Pro Gly Ile Ser Gly
                     -5
gtc tac cgg ctc ctt atg gcg aat gca acc cga aga gag agt gag gta
Val Tyr Arg Leu Leu Met Ala Asn Ala Thr Arg Arg Glu Ser Glu Val
            10
age etc ege ggg ttg gge agg gac gga gag ggg gee ege geg aet eca g
Ser Leu Arg Gly Leu Gly Arg Asp Gly Glu Gly Ala Arg Ala Thr Pro
<210> 386
<211> 281
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 199..279
<221> sig_peptide
<222> 199..267
<223> Von Heijne matrix
      score 5.09999990463257
      seg SLMVFLNLFFLNC/DP
<400> 386
tgtttatagg ttttaactct tatggttaga atggttgtga gtcatacgwg tgtcagacct
ctgctaattt cctcaggaca cattcccaga agtggaatta ccaagtcaaa gagcataaat
                                                                      120
actttagaga tacatgataa attgtgccag ctacctttcc aaaagagttg tactagttga
                                                                      180
ggtttctgcc agcagtat atg aca gtt ggg ctc cat att tta aga gat tca
                                                                      231
                    Met Thr Val Gly Leu His Ile Leu Arg Asp Ser
                                -20
cta atg gtg ttt ctc aac ctt ttt ttt tta aac tgt gac cca cac agg
                                                                      279
Leu Met Val Phe Leu Asn Leu Phe Phe Leu Asn Cys Asp Pro His Arg
        -10
                            - 5
99
                                                                      281
<210> 387
<211> 111
<212> DNA
<213> Homo sapiens
```

-220-															•
<220>															-
<221>								•							
<222>	51	09													
						*									•
<221>	sig_j	pept:	ide												
	56														
	Von		e ma	atrix	•						•				
~~~	scor					7									
						, ,									
	seq 1	MECVS	بالللاذ	IHAYF	יין אי				•						
<400>	387														
	atg gi Met Va	al Ar													49
	-	20	-			-1	-			•	-1				
	ac cat														97
Leu H	is His	s Ala	a Tyr	Pro	Leu	Pro	Ser	Thr	Met	Ile	Val	Ser	Phe	Pro	
-	5 .				1				5					10	
agg c	ct cc	cto	99												111
	ro Pro					Ţ.			•						
••••	-0		•			*								٠.,	
-210-	200											*			•
<210>															
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<212>		_													
<213>	Homo	sapi	ens												
<220>															
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	963	74													
(222)	30	, , =													•
000			٠.												
	sig_r		ae												
	961			_								•			
<223>	Von F	leijn	e ma	trix				•							
	score	5.0	9999	9904	6325	7									
	seq A	MVCF	GCPG	GASS	/RC						٠.				
	_														
<221s	misc_	feat	ure												•
<222>	_														
		a c	or	-											-
<223>	n=a,	g, c	OI.	L											
															·
<400>	388														
ttttg	gccgc	catg	tttt	cg to	cgca	gtaa	c tg	ccttg	ggtg	tcag	gtagt	ca 1	ttgc	cagttt	60
	gttct														113
- 333	<b>J</b>		•	<b>-</b>	_					Ala (					
								•		-25					
			1												
	tg gga														161
Trp V	al Gly	GIn	Xaa	Ser	Ser	Ala	Met	Val	Cys	Phe	Gly	Cys	Pro	Gly	
-20				-15					-10					-5	
aat a	cg tca	agt	cqc	tgc	cqc	tcc	cct	cqt	aaa	cat	caq	qcc	tca	aga	209
	la Ser														
·			1	-7.5	5		5	9	,	5	<b></b>	10	501	••••	
			_				_								
	cc cgc														257
Val P	ro Arg	Leu	Glu	Asn	Gly	Ala	Gln	Arg	Val	Val	Arg	Thr	Met	Val	
	15					20					25				
cac of	tg gtt	ttg	cag	cct	aaq	caa	gtc	act	tta	gta	cat	cct	cct	cac	305
	eu Val														
30					35	5		- ***		40				3	
		cc+	a++	+~-			<b>5 -</b> -	~					<b>.</b>	<b>.</b>	
	tg gag														353
Gly L	eu Glu	Pro	vaı		Thr	Pro	Ile	Ala		Met	Xaa	Pro	Lys		
45	-			50					55					60	
C2C 0		202		A A											
cac g	gg ctc ly Leu	aya	agt	CCC	ttg										374

212 65 <210> 389 <211> 192 <212> DNA <213> Homo sapiens . <220> <221> CDS <222> 52..192 <221> sig\_peptide <222> 52..153 <223> Von Heijne matrix score 5.09999990463257 seq PXLLSXLHGLLYG/SP <400> 389 ggcagacttc aaccaggctg tgggaggaga gctcagtggg gcacagagaa g atg ggt 57 Met Gly gtt gtc agt ggg ggt gtt ggt gac ttg acc aca aaa acc caa gag aat 105 Val Val Ser Gly Gly Val Gly Asp Leu Thr Thr Lys Thr Gln Glu Asn -30 -25 -20 ggg ctc tta cca gvc cty ctc tcc wkc ctk cac gga ctg ctc tat ggc 153 Gly Leu Leu Pro Xaa Leu Leu Ser Xaa Leu His Gly Leu Leu Tyr Gly -15 -10 age cet gat gea gar etc acg gge eeg gat eec tgg gat 192 Ser Pro Asp Ala Glu Leu Thr Gly Pro Asp Pro Trp Asp 10 <210> 390 <211> 371 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 321..371 <221> sig\_peptide <222> 321..365 <223> Von Heijne matrix score 5.09999990463257 seq FLSXTCVLSCXRS/LS <400> 390 totgttcagg ttttgtattt gttcatagta taatcttggt ttgtaggttg tgtgtatctg 60 ggaagaaact ttacaatctc taacaggcct ggaaggtcta atctataaaa gtatttcatt 120 gaccttgaag aaggtcaatt atttatataa gaaaataaac tcaacatttt atccataaaa 180 aatgtaattc cggaatttat gttagtaaaa ttataacact gataacataa aaagtgctat 240 taatccttaa gaaagagtta ccttttcttt tctatcttca tcacagctag cccagtctta 300 gtctatttca ttagcttcct atg ggc ttc ctc tca ckt aca tgc gtg ctc tct 353 Met Gly Phe Leu Ser Xaa Thr Cys Val Leu Ser -15 -10 tgc dtg cgc tcg ctc tct 371 Cys Xaa Arg Ser Leu Ser

<210> 391 <211> 328 <212> DNA <213> Homo sapiens

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 <222> 184..327
 <221> sig_peptide
 <222> 184..300
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      seq LVCFFNSVSFLFG/VS
 <400> 391
ccgttatgtg ttcagctcaa ttagattaat taccttcctc accaggagtc acaatgcttt
                                                                     60
gcagtttatc tgcggtaact aaatgttagt tttgtaagta aaaggtactg ttattgacct
                                                                    120
cgaaagggct atagttcctt tgaacttaca gagaagagtt ccaaacaact atttctaacc
                                                                    180
aag atg gaa tat ggg tca gca aaa ttg tct tca ggt aga gtt ttc tac
                                                                    228
    Met Glu Tyr Gly Ser Ala Lys Leu Ser Ser Gly Arg Val Phe Tyr
                    -35
                                       -30
ttg cca aga gac ttt ggc att gag agg aga gtt ctt gtt tgt ttt
                                                                    276
Leu Pro Arg Asp Phe Gly Ile Glu Arg Arg Val Leu Val Cys Phe Phe
                -20
                                   -15
aac tot gta toa ttt otg ttt ggt gto tot ara aaa aaa too gra caa
                                                                    324
Asn Ser Val Ser Phe Leu Phe Gly Val Ser Xaa Lys Lys Ser Xaa Gln
tgg g
                                                                    328
Trp
<210> 392
<211> 303
<212> DNA
<213> Homo sapiens
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<221> CDS
<222> 252..302
<221> sig_peptide
<222> 252..290
<223> Von Heijne matrix
      score 5
      seq MLSGLVLNSWALA/YQ
<400> 392
60
attaatttag agacagggtc tcactatgtc acccaggctg tagtgcagtg gtgcaatcat
                                                                   120
ggctcactgt agccttgacc tcccaggctc aagcaatctt cctacctcag cctctcaggc
                                                                   180
agctgggact acagacccac agcactacgc ctgacttatg attttattt ttgtggagac
                                                                   240
agggtcttac t atg ttg tct ggg ctt gtc tta aac tct tgg gcc tta gcc
                                                                   290
            Met Leu Ser Gly Leu Val Leu Asn Ser Trp Ala Leu Ala
                        -10
tac caa cta gct g
                                                                   303
Tyr Gln Leu Ala
<210> 393
<211> 366
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<213> Homo sapiens
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<222> 298..366
<221> sig_peptide
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<222> 298..345
<223> Von Heijne matrix
      score 5
      seq VFFXGXSIILVLG/ST
<221> misc feature
<222> 265
<223> n=a, g, c or t
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tttttccccg cccctgagac cctgcagcac catctgtcat ggcggctggg ctgtttggtt
tgagegeteg cegtettttg geggeagegg egaegegagg geteeeggee geeegegtee
                                                                       120
gctgggaatc tagcttctcc argamytgtg gtcgccccgt ccgctgtggc gggaaagcgg
                                                                       180
tccccagaac cgaccacacc gtggcaagag gacccagaac ccgaggacga aaacttgtat
                                                                       240
gagaagaasc cagactccca tggknatgac aaggaccccg ttttggacgt ctggaac
                                                                       297
atg ega ett gte tte tte ktw gge gks tee ate ate etg gte ett gge
                                                                       345
Met Arg Leu Val Phe Phe Xaa Gly Xaa Ser Ile Ile Leu Val Leu Gly
    -15
                         -10
age acc ttt gkg gcc tat ctg
                                                                       366
Ser Thr Phe Xaa Ala Tyr Leu
<210> 394
<211> 126
<212> DNA
<213> Homo sapiens
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<222> 21..125
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<222> 21..68
<223> Von Heijne matrix
      score 5
      seq SDFFLLFVSLSLS/PF
agettggeat ataggeteaa atg tta tea tea gat tit tit etc etc tit gte
                                                                        53
                      Met Leu Ser Ser Asp Phe Phe Leu Leu Phe Val
                          -15
tet tta tet tta tet cca ttt cet ttt ttt ett ttt ect cee ete ttt
                                                                      101
Ser Leu Ser Leu Ser Pro Phe Pro Phe Leu Phe Pro Pro Leu Phe
tcc tgc ttt ctc tta ccc acc cgg g
                                                                      126
Ser Cys Phe Leu Leu Pro Thr Arg
            15
<210> 395
<211> 329
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 154..327
<221> sig_peptide
<222> 154..195
<223> Von Heijne matrix
      score 5
      seq FIAALFTVAKIWN/QP
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<400> 395
tgaaaatgta aattagtgca gttattatgg magtcagtat ggaacttcct caaaaaacta
                                                                        60
acaataaaac tcccatatga tccagcaatc ctaccactgr atatttatcc aaaggaaagg
                                                                       120
aagteggtat atttaacagg catetgcace eec atg tit att gea gea eta tie 1
                                      Met Phe Ile Ala Ala Leu Phe
                                                       -10
aca gta gcc aag ata tgg aat caa cct aaa tgt cca tca acg gat gaa
                                                                       222
Thr Val Ala Lys Ile Trp Asn Gln Pro Lys Cys Pro Ser Thr Asp Glu
tgg ata aat aaa atg tgg tac ata tac aca atg gag tac tat cca gac
                                                                       270
Trp Ile Asn Lys Met Trp Tyr Ile Tyr Thr Met Glu Tyr Tyr Pro Asp
10
                    . 15
                                         20
ata aaa aag aat gga att ctg aca ttt aag gca aca agg atg aac cgg
                                                                       318
Ile Lys Lys Asn Gly Ile Leu Thr Phe Lys Ala Thr Arg Met Asn Arg
                 30
                                     35
aag aca tta tg
                                                                       329
Lys Thr Leu
<210> 396
<211> 99
<212> DNA
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      score 5
      seg VCGCLCVWMCVCG/XV
<221> misc_feature
<222> 49
<223> n=a, g, c or t
<400> 396
gtat atg tgt gtg tgt ggg tgt tta tgt gtg tgg atg tgt gtg tgt ggn
                                                                        49.
     Met Cys Val Cys Gly Cys Leu Cys Val Trp Met Cys Val Cys Gly
with gtg tgt ata tac ata tgm gtg tat gtg tgt aca tgt gtg agg ggg
                                                                        97
Xaa Val Cys Ile Tyr Ile Xaa Val Tyr Val Cys Thr Cys Val Arg Gly
1
ga
                                                                        99
<210> 397
<211> 316
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 134..316
<221> sig peptide
<222> 134..211
<223> Von Heijne matrix
     score 5
     seq LSLFVFFWLVGFS/FF
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<221> misc\_feature

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 <222> 10..75
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           Met Gln Phe Thr Val Leu Met Cys Pro Val Gln Trp Leu Leu
                    -20
                                        -15
 gtg tat tca ccc agt tgt gca gcc acc atc aca gtc aat ttt aaa aca
                                                                         99
 Val Tyr Ser Pro Ser Cys Ala Ala Thr Ile Thr Val Asn Phe Lys Thr
             - 5
 ttt tca tca ccc caa acc ggg
                                                                        120
 Phe Ser Ser Pro Gln Thr Gly
 <210> 400
 <211> 463
 <212> DNA
 <213> Homo sapiens
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 <221> CDS
 <222> 342..461
 <221> sig_peptide
 <222> 342..452
 <223> Von Heijne matrix
      score 5
       seq VSCLSAGLRVCCS/QR
 <221> misc_feature
 <222> 246,260
 <223> n=a, g, c or t
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 ctctgtcccc gcggctgggt ctcgtctgct ccggttcctg ggctcctaat tcttggtcca
                                                                        60
 gettetteca ggcacateet ettetetgee eteegteeat tttggageeg gagatggtgg
                                                                       120
 gctkggggcc gccccagtag tgagacagtg gaagtaaacc ccatctgccg ttcccgtgcg
                                                                       180
 tagagaaaaa cgttgaccgc gaggctgggg aggagagttg cctctgagga agaagggcac
                                                                       240
 agaganccaa aattagtttn gaaagcatcc tgatttggtg cccgaggcct ggaaagaaat
                                                                       300
 ggcggctggg gtgcggcgga ggtaggggag gaaaacgttg g atg aga agg gcc tgg
                                                                       356
                                               Met Arg Arg Ala Trp
 act cag gaa agg gaa ccg cgt ccg tgt gag ccc gct gag cgc gca gac
                                                                       404
 Thr Gln Glu Arg Glu Pro Arg Pro Cys Glu Pro Ala Glu Arg Ala Asp
                             -25
                                                 -20
 cet gee cet gte tee tgt etg tet gea ggt etg ege gte tgt tgt tee
                                                                       452
 Pro Ala Pro Val Ser Cys Leu Ser Ala Gly Leu Arg Val Cys Cys Ser
 cag cgc tct gc
                                                                       463
Gln Arg Ser
 <210> 401
<211> 206
 <212> DNA
 <213> Homo sapiens
 <220>
<221> CDS
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60

114

162

206

104

152

200

248

296

330

WO 99/53051 218 <222> 94..204 <221> sig\_peptide <222> 94..168 <223> Von Heijne matrix score 4.90000009536743 seq DFFICLLAICVSS/FE <400> 401 tactgtttat tgattctttg attatggcca ttcttacagg agtaaggtgg tatcacactg tggttttgat ttgcatttcc ctgatcatta gtg atg ttg cat ttg att tgc att Met Leu His Leu Ile Cys Ile -25 -20 tee etg ate gtt aat gat tit tie ata tgt tig tig gee att tge gta Ser Leu Ile Val Asn Asp Phe Phe Ile Cys Leu Leu Ala Ile Cys Val -15 -10 tot tot tit gag aat tgt cta tit atg too tta goo cac agt gg Ser Ser Phe Glu Asn Cys Leu Phe Met Ser Leu Ala His Ser 1 <210> 402 <211> 330 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 42..329 <221> sig\_peptide <222> 42..230 <223> Von Heijne matrix score 4.90000009536743 seq VTSLANLIPPVKA/XP <400> 402 · acagggetee actgeagtta ggageeggtg agteegggtg g atg agg tea gag ege Met Arg Ser Glu Arg ece atg gtg tgg tgc tgc etc ttt gtc egt teg eag ega aaa egg aaa Pro Met Val Trp Cys Cys Leu Phe Val Arg Ser Gln Arg Lys Arg Lys -55 -50 cag age ace caa gat gaa gat get gtt age ett tge agt ete gae ata Gln Ser Thr Gln Asp Glu Asp Ala Val Ser Leu Cys Ser Leu Asp Ile -40 -35 agt gag cct agt aat aaa cgg gtc aaa ccc ctt tcc cga gtc acg tcg Ser Glu Pro Ser Asn Lys Arg Val Lys Pro Leu Ser Arg Val Thr Ser -20 cta gca aac ctc atc ccg ccc gtg aag gcc ayg cca tta aag cgc ttc Leu Ala Asn Leu Ile Pro Pro Val Lys Ala Xaa Pro Leu Lys Arg Phe -10 - 5 agt caa acc ctg cag cgc tcc att agc ttc cgc agt gag agt cgc cct

Ser Gln Thr Leu Gln Arg Ser Ile Ser Phe Arg Ser Glu Ser Arg Pro

gac atc ctc gcc ccc cga ccc tgg tcc aga aat g

Asp Ile Leu Ala Pro Arg Pro Trp Ser Arg Asn

<210> 403 <211> 311 <212> DNA

<213> Homo sapiens

25

10

<213> Homo sapiens

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<220>
<221> CDS
<222> 168..311
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<222> 168..227
<223> Von Heijne matrix
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      seq CILISTAFPSLLT/QI
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tgagcagatg gtgccaggat ttaaacctat gtttatcaga tgcagatgac ccaaacagtg
                                                                        60
gcttatctgt tggtaatttt tatttagatc aagttaaaca taaatgactt tgcattactc
                                                                       120
tttggtcact ttttcctagt catttcaaat agtctgtctt atttctc atg gtt ttt
                                                                       176
                                                     Met Val Phe
                                                     -20
tgg aca aaa ttt tgt att tta att agt aca gca ttt cct tct tta ttg
                                                                       224
Trp Thr Lys Phe Cys Ile Leu Ile Ser Thr Ala Phe Pro Ser Leu Leu
        -15
aca cag att att ttc cct aaa tct att aca ttt gct ttc cag ttt ttc
                                                                       272
Thr Gln Ile Ile Phe Pro Lys Ser Ile Thr Phe Ala Phe Gln Phe Phe
tgg aac agg gaa aaa caa aaa aca aca cca act ggg
                                                                       311
Trp Asn Arg Glu Lys Gln Lys Thr Lys Thr Pro Thr Gly
                20
<210> 404
<211> 274
<212> DNA
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<222> 80..274
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<223> Von Heijne matrix
      score 4.90000009536743
      seq MLIMLGIFFNVHS/AV
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ccctgcgagg gcatcctggg ctttctccca ccgctttccg agcccgcttg cacctcggcg
                                                                        60
atcoccgact coeffeth atg gcg tcg ctc ctg tgc tgt ggg ccg aag ctg
                                                                       112
                     Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu
                             -35
                                                  -30
gcc gcc tgc ggc atc gtc ctc agc gcc tgg gga gtg atc atg ttg ata
                                                                       160
Ala Ala Cys Gly Ile Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile
                        -20
                                             -15
atg ctc gga ata ttt ttc aat gtc cat tcc gct gtg ttg att gag gac
                                                                       208
Met Leu Gly Ile Phe Phe Asn Val His Ser Ala Val Leu Ile Glu Asp
                    -5
gtt ccc ttc acg gag aaa gat ttt gag aat ggc ccc cag aac ata tac
                                                                       256
Val Pro Phe Thr Glu Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr
            10
                                15
aac ctt tac gag cat ggg
                                                                       274
Asn Leu Tyr Glu His Gly
        25
<210> 405
<211> 153
<212> DNA
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 <221> CDS
 <222> 69..152
 <221> sig peptide
 <222> 69..116
 <223> Von Heijne matrix
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       seq SALLLEXLQXAIP/RX
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 geceaaga atg tet gte tea get etg ett eta gag mte ete eaa gmt gee
                                                                       . 110
          Met Ser Val Ser Ala Leu Leu Leu Glu Xaa Leu Gln Xaa Ala
                                   -10
 atc cct cgy mam acc tca ggc ttm caa gac ctg ccc aac tgg g
                                                                        153
 Ile Pro Arg Xaa Thr Ser Gly Xaa Gln Asp Leu Pro Asn Trp
 <210> 406
 <211> 206
 <212> DNA
 <213> Homo sapiens
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 <221> CDS
 <222> 57..206
 <221> sig_peptide
 <222> 57..173
 <223> Von Heijne matrix
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       seq VIAIVSFTTLCSS/LY
 <400> 406
· aaataaaaaa tattaaaaaa taatctcatc tttgatttta gatttagggg gtgtgc atg
                                                                        59
 cag gct tgt tat atg ggt atg tgg tat act gcc gag gct tgg ggt acg
                                                                        107
 Gln Ala Cys Tyr Met Gly Met Trp Tyr Thr Ala Glu Ala Trp Gly Thr
 att gag tcc ctc acc cag gta gtg agc gta atc gca ata gtt agt ttt
                                                                        155
 Ile Glu Ser Leu Thr Gln Val Val Ser Val Ile Ala Ile Val Ser Phe
                             -15
                                                  -10
 aca acc ctg tgc tcc tct ctg tat tcc ccc caa gta gtc ccc agt gtt
                                                                        203
 Thr Thr Leu Cys Ser Ser Leu Tyr Ser Pro Gln Val Val Pro Ser Val
     -5
 999
                                                                        206
 Gly
 <210> 407
 <211> 479
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 <222> 277..477
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 <222> 277..462
 <223> Von Heijne matrix
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## seq PLAACPLLLPIFS/HA

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<210> 409 <211> 341

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<212> DNA
 <213> Homo sapiens
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 <221> sig_peptide
 <222> 94..216
 <223> Von Heijne matrix
       score 4.90000009536743
       seq LSLVSHAPGEALA/RA
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                                                                        60
ttggagetge tgctaaataa tttetgetea gee atg teg eeg get eea gat gea
                                                                       114
                                      Met Ser Pro Ala Pro Asp Ala
gcc ccg gct cct gcg tcg atc tcc ctg ttt gac ctc agc gcg gat gct
                                                                       162
Ala Pro Ala Pro Ala Ser Ile Ser Leu Phe Asp Leu Ser Ala Asp Ala
                 -30
                                     -25
ccg gtc ttt cag ggc ctg agc ctg gtg agc cac gcg cct ggg gag gct
                                                                       210
Pro Val Phe Gln Gly Leu Ser Leu Val Ser His Ala Pro Gly Glu Ala
             -15
                                -10
ctg gcc cgg gct ccg cgt act tcc tgt tca ggc tca ggg gag aga gaa
                                                                       258
Leu Ala Arg Ala Pro Arg Thr Ser Cys Ser Gly Ser Gly Glu Arg Glu
ago coa gaa aga aag ota oto cag ggt oot atg gat att toa gag aag
                                                                       306
Ser Pro Glu Arg Lys Leu Leu Gln Gly Pro Met Asp Ile Ser Glu Lys
                    20
                                                              30
tta ttt tgt tca act tgt gac cag acc ttc cag aa
                                                                       341
Leu Phe Cys Ser Thr Cys Asp Gln Thr Phe Gln
                35
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<222> 153..320
<221> sig_peptide
<222> 153..257
<223> Von Heijne matrix
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      seq LFIFIGSLQPVPT/RF
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cacacacaaa ctctcaagtg gcctaattcc ctctcaccaa accaatcaca atacagataa
                                                                       60
aagagaataa cttgtgttca tttttgtaca aacaaaaaag atataaattg tgaatgrtgc
                                                                      120
atgrttttta awtwmccaag taaactgggc aa atg ctt ctg cat tat tta aag
                                                                      173
                                    Met Leu Leu His Tyr Leu Lys
                                    -35
cta aaa ggt gat cag tgg aaa ctt tcc tct gtt agt act cta ata ctt
                                                                      221
Leu Lys Gly Asp Gln Trp Lys Leu Ser Ser Val Ser Thr Leu Ile Leu
            -25
                                -20
ttt ata ttt atc ggc tca cta caa cct gtg cct acc agg ttc aag cga
                                                                      269
Phe Ile Phe Ile Gly Ser Leu Gln Pro Val Pro Thr Arg Phe Lys Arg
        -10
                            - 5
ttc tcc tgt ctc gdc cac ctg agt agc cga gac cac agg caa gca cta
                                                                      317
Phe Ser Cys Leu Xaa His Leu Ser Ser Arg Asp His Arg Gln Ala Leu
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5 cgg Arg	_				10					15					20	321
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	1 > C	DS 46	35								•	٠				
<22	2 > 8 3 > V s	45 on H core	642 Teijn : 4.9	de ne ma 0000 AAVA	trix 0095	3674	3 .					,				
	0 > 4									•						
gggt	ttgt	ggt	cato	gtgc	99 9 ag a	tttc	ggtt ta a	g ga	ggac	tcgt	tgg	ggag	gtg	gcct	gcgctt cc aac	60
gca	gaga	cig		cccg	<u></u>	M	et A	la G	lu G	ga g ly A 150	sp A	sn A	rg S	er T	cc aac hr Asn 145	113
ctg	ctg	gct	gca	gag	act	gca	agt	ctg	gaa	gaa	cag	ctg	caa	qqa	taa	161
Leu	Leu	Ala	Ala -14	Glu 0	Thr	Ala	Ser	Leu -13	Glu 5	Glu	Gln	Leu	Gln -13	Gly 0	Trp	
Gly	Glu	Val -12	Met 5	ctg Leu	Met	Ala	Asp -12	Lys 0	Val	Leu	Arg	Trp	Glu 5	Arg	Ala	209
Trp	Phe	Pro 0	Pro	gcc Ala	Ile	Met -10	Gly 5	Val	Val	Ser	Leu -10	Val	Phe	Leu	Ile	257
Ile -95	Tyr	Tyr	Leu	gat Asp	Pro -90	Ser	Val	Leu	Ser	Gly -85	Val	Ser	Cys	Phe	Val -80	305
Met	Phe	Leu	Cys	ttg Leu -75	Ala	Asp	Tyr	Leu	Val -70	Pro	Ile	Leu	Ala	Pro	Arg	353
Ile	Phe	Gly	Ser -60	aat Asn	Lys	Trp	Thr	Thr	Glu	Gln	Gln	Gln	Arg -50	Phe	His	401
Glu	Ile	Cys -45	Ser	aat Asn	Leu	Val	Lys -40	Thr	Arg	Arg	Arg	Ala -35	Val	Gly	Trp	449
Trp	Lys -30	Arg	Leu	ttc Phe	Thr	Leu -25	Lys	Glu	Glu	Lys	Pro -20	Lys	Met	Tyr	Phe	497
atg	acc	atg	atc	gtt	tcc	ctt	gct	gcg	gtt	gct	tgg	gtg	gga	caa	caa	545
-15				Val	-10					-5			_		1	
Val	His	Asn	Leu 5	ctt Leu	Leu	Thr	Tyr	Leu 10	Ile	Val	Thr	Ser	Leu 15	cta Leu	ttg Leu	593
ctt Leu	cct Pro	gga Gly 20	cta Leu	aac Asn	caa Gln	cat His	gga Gly 25	atc Ile	att Ile	ttg Leu	aag Lys	tac Tyr 30	att Ile			635
	> 41 > 33															

<212> DNA

<213> Homo sapiens

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<220>
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 <222> 33..335
<221> sig_peptide
<222> 33..110
<223> Von Heijne matrix
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                                                                        53
                                     Met Ala Ala Leu Lys Ala Leu
                                         -25
gtg tcc ggc tgt ggg cgg ctt ctc cgt ggg cta cta gcg ggc ccg gca
                                                                       101
Val Ser Gly Cys Gly Arg Leu Leu Arg Gly Leu Leu Ala Gly Pro Ala
                -15
                                     -10
gcg acc agc tgg tct cgg ctt cca gct cgc ggg ttc agg gaa gtg gtg
                                                                       149
Ala Thr Ser Trp Ser Arg Leu Pro Ala Arg Gly Phe Arg Glu Val Val
gag acc caa gaa ggg aag aca act ata att gaa ggc cgt atc aca gcg
                                                                       197
Glu Thr Gln Glu Gly Lys Thr Thr Ile Ile Glu Gly Arg Ile Thr Ala
                         20
act ccc aag gag agt cca aat cct cct aac ccc tct ggc cag tgc ccc
                                                                       245
Thr Pro Lys Glu Ser Pro Asn Pro Pro Asn Pro Ser Gly Gln Cys Pro
                    35
                                         40
ate tgc cgt tgg aac etg aag cac aag tat aac tat gac gat gtt etg
                                                                       293
Ile Cys Arg Trp Asn Leu Lys His Lys Tyr Asn Tyr Asp Asp Val Leu
                50
                                     55
ctg ctt agc cag ttc atc cgg cct cat gga ggc atg ctg ccc
                                                                       335
Leu Leu Ser Gln Phe Ile Arg Pro His Gly Gly Met Leu Pro
<210> 413
<211> 158
<212> DNA
<213> Homo sapiens
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<221> CDS
<222> 25..156
<221> sig_peptide
<222> 25..93
<223> Von Heijne matrix
      score 4.90000009536743
      seq LVGFKQVVAWTFA/SD
<221> misc feature
<222> 17
<223> n=a, g, c or t
agaaactgac atttgbntgt ttta atg ggg tcc ctg ctg ttc atc agg cag
                                                                       51
                           Met Gly Ser Leu Leu Phe Ile Arg Gln
                                        -20
aca ctt gtg ggc ttt aaa cag gtc gtt gct tgg acc ttt gct tct gat
                                                                       99
Thr Leu Val Gly Phe Lys Gln Val Val Ala Trp Thr Phe Ala Ser Asp
tca cat tgt gsa aaw gtg gww atg gtd wtc tws agt cag ttg arw aat
                                                                      147
Ser His Cys Xaa Xaa Val Xaa Met Val Xaa Xaa Ser Gln Leu Xaa Asn
                            10
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Met Asn Ala Ser Leu Leu Ser Phe Cys

220

229

-15

ctt tgt tca gat ttc atc tct caa gat gcc ctc ctt ctc act gtc ata

Leu Cys Ser Asp Phe Ile Ser Gln Asp Ala Leu Leu Leu Thr Val Ile

ttt cct ccc

Phe Pro Pro

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 <213> Homo sapiens
<220>
 <221> CDS
 <222> 27..263
 <221> sig_peptide
 <222> 27..206
 <223> Von Heijne matrix
       score 4.90000009536743
       seg LVGVIVHSGQAHA/GH
 <400> 416
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                                                                        53
                              Met Leu Asn Met Glu Pro Tyr Thr Val
                              -60
                                                   -55
tca gga atg gct cgc caa gat tct tct tct gaa gtt ggg gaa aat ggg ,
                                                                       101
Ser Gly Met Ala Arg Gln Asp Ser Ser Ser Glu Val Gly Glu Asn Gly
                         -45
                                             -40
cga agt gtg gat cag ggc ggt gga gga tcc cca cga aaa aag gtt gcc
                                                                       149
Arg Ser Val Asp Gln Gly Gly Gly Ser Pro Arg Lys Lys Val Ala
-35
                     -30
                                         -25
ctc aca gaa aac tat gaa ctt gtc ggt gtc atc gta cac agt ggg cag
                                                                       197
Leu Thr Glu Asn Tyr Glu Leu Val Gly Val Ile Val His Ser Gly Gln
                 -15
                                     -10
gca cac gca ggc cac tac tat tcc ttc att aag gac agg cga ggg tgt
                                                                       245
Ala His Ala Gly His Tyr Tyr Ser Phe Ile Lys Asp Arg Arg Gly Cys
gga aaa gga aag tgg ctg gg
                                                                       265
Gly Lys Gly Lys Trp Leu
    15
<210> 417
<211> 228
<212> DNA
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<221> CDS
<222> 160..228
<221> sig_peptide
<222> 160..219
<223> Von Heijne matrix
      score 4.90000009536743
      seq LHLXSSRXPPILA/SP
<221> misc_feature
<222> 166..167,190
<223> n=a, g, c or t
<400> 417
ttgtctgtct taggcctgga cactgttgtt gacttatttc cagattttaa tttctctttg
                                                                       60
gttgaagact gccaactgtc tcatagagtg tttgatttat ttatttatty athtwgacat
                                                                      120
gaggwykctc tctgcmaacc caggctggak tgcagtgac atg atv nng gct cac
                                                                      174
                                           Met Xaa Xaa Ala His
                                           -20
tto ago oto cac oto nkg ago toa agg art ook ooc ato tta goo too
                                                                      222
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Phe Ser Leu His Leu Xaa Ser Ser Arg Xaa Pro Pro Ile Leu Ala Ser
 -15
                      -10
 cca gta
                                                                        228
 Pro Val
 <210> 418
 <211> 225
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 <222> 125..223
 <221> sig_peptide
 <222> 125..175
 <223> Von Heijne matrix
       score 4.90000009536743
       seq VCELSIFFTYVLA/IY
 aaaagtttgt aataagttgc actttcatca agactgtatt agggagtcca gtctccccac
                                                                         60
 atccttgtca gcacgggatg acatcagtct tttaaatctt accaacttat tgggaaaaaa
                                                                        120
 aaaa atg ata cgt cct gtt tgt gaa ttg agc att ttt ttc acc tat gta
                                                                        169
      Met Ile Arg Pro Val Cys Glu Leu Ser Ile Phe Phe Thr Tyr Val
              -15
                                   -10
 cta gcc att tac ata tct cct tct gtg aat tgt ctg ttt ata tcc ttt
                                                                        217
 Leu Ala Ile Tyr Ile Ser Pro Ser Val Asn Cys Leu Phe Ile Ser Phe
                                              10
 cct gcg gg
                                                                        225
 Pro Ala
 15
 <210> 419
 <211> 293
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> CDS
 <222> 42..293
<221> sig_peptide
 <222> 42..128
 <223> Von Heijne matrix
       score 4.80000019073486
       seq LLSARLLSQEKRA/AE
<400> 419
gtgctctatg gagctattgc ggccgtgggt ggtcgcgggc r atg cgg ggc tgc cag
                                                                        56
                                               Met Arg Gly Cys Gln
ctc ctc ggg ctt cgt agc tct tgg ccc ggg gac cta cta agt gct cgg
                                                                       104
Leu Leu Gly Leu Arg Ser Ser Trp Pro Gly Asp Leu Leu Ser Ala Arg
                 -20
                                     ~15
ctc ttg tcc caa gag aag cgg gca gcg gaa acg cac ttt ggg ttt gag
                                                                       152
Leu Leu Ser Gln Glu Lys Arg Ala Ala Glu Thr His Phe Gly Phe Glu
             -5
act gtg tcg gaa gag gag aag agg ggg gac tta aca tca gtt gta agt
                                                                       200
Thr Val Ser Glu Glu Glu Lys Arg Gly Asp Leu Thr Ser Val Val Ser
                         15
                                             20
cta gag tac cct gaa gtg caa tta cag ggt caa agg gtc tat gcm ttc
                                                                       248
Leu Glu Tyr Pro Glu Val Gln Leu Gln Gly Gln Arg Val Tyr Ala Phe
```

```
30
                                         35
 ctg tca ccc att tgt acc tat ggc tct gag gga tgc agc ctc aag
                                                                       293
 Leu Ser Pro Ile Cys Thr Tyr Gly Ser Glu Gly Cys Ser Leu Lys
                                     50
 <210> 420
 <211> 194
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> CDS
 <222> 30..194
 <221> sig_peptide
 <222> 30..134
 <223> Von Heijne matrix
       score 4.80000019073486
       seg PWVLDIFLTLVFA/LG
<400> 420
 agttgctaga aagcaatgcg cctattcac atg gag aat ctt ccc ttt cct cta
                                                                        53
                               Met Glu Asn Leu Pro Phe Pro Leu
                                 -35
aaa tta ctt agt gcc tca tca cta aac acc ccc agc tcc aca cca tgg
Lys Leu Leu Ser Ala Ser Ser Leu Asn Thr Pro Ser Ser Thr Pro Trp
                             -20
gtg ttg gat atc ttc ctc acc ttg gtg ttt gcc ctg ggg ttc ttc ttc
                                                                      149
Val Leu Asp Ile Phe Leu Thr Leu Val Phe Ala Leu Gly Phe Phe
                        -5
cta tta ctc ccc tac ttc tct tac ctc cgt tgt gac aac cca cca
                                                                      194
Leu Leu Pro Tyr Phe Ser Tyr Leu Arg Cys Asp Asn Pro Pro
                 10
<210> 421
<211> 90
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 29..88
<221> sig peptide
<222> 29..67
<223> Von Heijne matrix
      score 4.80000019073486
      seq MCVCVFAIFGVRC/CV
<221> misc feature
<222> 61
<223> n=a, g, c or t
tatttgggat ttgttgctct gtgtgtat atg tgc gtg tgt gtg ttt gct ata
                                                                       52
                               Met Cys Val Cys Val Phe Ala Ile
                                           -10
ttt ggg gtn cgt tgc tgt gtg tgt gtc cgc tgt att tg
Phe Gly Val Arg Cys Cys Val Cys Val Arg Cys Ile
-5
```

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<211> 161
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 22..159
<221> sig peptide
<222> 22..153
<223> Von Heijne matrix
      score 4.80000019073486
      seq XPCPLLFPGACFP/CP
<400> 422
tcatttgggt ttttatttaa t atg att tgc ata ttt tac tct aag att tcc
                                                                        51
                         Met Ile Cys Ile Phe Tyr Ser Lys Ile Ser
                                         -40
atc tct gtc ggc tgt ggg agg aca gcc gag caa gtt gga tgt aaa
                                                                        99
Ile Ser Val Gly Cys Gly Arg Thr Ala Ala Glu Gln Val Gly Cys Lys
                 -30
                                     -25.
cag agg tca ttt cac ckc ccy tgc cct ctg ctg ttt cct ggt gcd tgc
                                                                       147
Gln Arg Ser Phe His Xaa Pro Cys Pro Leu Leu Phe Pro Gly Ala Cys
                                -10
ttt ccc tgc cca ac
                                                                       161
Phe Pro Cys Pro
        1
<210> 423
<211> 420
<212> DNA
<213> Homo sapiens
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<221> CDS
<222> 333..419
<221> sig_peptide
<222> 333..380
<223> Von Heijne matrix
      score 4.80000019073486
      seq ICVSLMASDGASS/PV
<221> misc_feature
<222> 323..324,328
<223> n=a, g, c or t
<400> 423
ctgccgcygg acacgggttc ttccagcttt tggctattgt gaataacgct gctatggaca
                                                                       60
tgaatgtaca aacatccctt cagatcctcc tttcagttct tgtgggtaca taccccgagt
                                                                      120
ggaactgtgg catcatatgg taactctgtg tttaacattt tgaggaacca ccctactgct
                                                                      180
tcccacagag gctgtaccag tttacttccc accaacagtg caaggattcc aatttctcca
                                                                      240
catccgtgcc aacactattt tctttttgtc gctgttgtca ttgtttgtct ggaaaatagc
                                                                      300
catgctgagg ggtgagaggt grnnghanrg tt atg aat ttg att tgc gtt tcc
                                                                      353
                                    Met Asn Leu Ile Cys Val Ser
                                        -15
ctg atg gcc agt gat ggg gca tct tcc cct gtg ctt ggt ggc tct tca
                                                                      401
Leu Met Ala Ser Asp Gly Ala Ser Ser Pro Val Leu Gly Gly Ser Ser
                - 5
                                    1
cac tct tcc tcc cwt rgg g
                                                                      420
His Ser Ser Ser Xaa Xaa
       10
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<210> 424
<211> 432
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 256..432
<221> sig_peptide
<222> 256..396
<223> Von Heijne matrix
     score 4.80000019073486
     seg LVSALPQASFSSS/SE
<400> 424
gagagagaga 999agagaga agagagggag gagggaagaa gaaaagacgg agggaggtga
                                                                 120
ggaggaaggg agggggagag acagagacct agaggggctg aagacccaga cagagctggc,
                                                                 180
agagctactg agaagaggac tggagcgctc tgagagcctc tcaagatctt ttgggggagc'
ccaataaatg tgaac atg gga tot gtc acr gga got gtc otc aag acg cta
                                                                 291
                Met Gly Ser Val Thr Gly Ala Val Leu Lys Thr Leu
                       -45
                                          -40
ctt ctg tta tct act caa aat tgg aac aga gtc gaa gct ggg aat tcc
                                                                 339
Leu Leu Ser Thr Gln Asn Trp Asn Arg Val Glu Ala Gly Asn Ser
                   -30
                                      -25
tat gac tgt gat gat cot ott gtg tot gcc ttg cot cag gca too tto
                                                                 387
Tyr Asp Cys Asp Asp Pro Leu Val Ser Ala Leu Pro Gln Ala Ser Phe
               -15
                                 -10
age agt tet tee gag ete tee age agt eat agt eet gga tit gea
                                                                 432
Ser Ser Ser Ser Glu Leu Ser Ser Ser His Ser Pro Gly Phe Ala
<210> 425
<211> 419
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 278..418
<221> sig_peptide
<222> 278..370
<223> Von Heijne matrix
     score 4.80000019073486
     seq FFLLFLFSSCDVP/VP
<400> 425
ccgaattatt ttagtgttac ttatctttga ataaaatgta tttttcttgg atcaattagt
                                                                  60
120
tctagatcac agtgaagctt taatatggkk ggatatttgt cccagcccaa atcccatgct
                                                                 180
gaattgaaac ccctagtgct ggaggtgggg cctggtggaa ggtgtttgga tcatqaggac
                                                                 240
acatetetga tgaatggeet ageteateet ettagtg atg atg agt gag tye tea
                                                                 295
                                      Met Met Ser Glu Xaa Ser
caa gat ctg gtt gta aag tgt gcc cca cca csg cca ttc ttt ctc ttq
                                                                 343
Gln Asp Leu Val Val Lys Cys Ala Pro Pro Xaa Pro Phe Phe Leu Leu
                  -20
                                     -15
ttc ctg ttt tct tca tgt gat gtg cct gtt ccc ctt cac ctt ctg caa
                                                                 391
Phe Leu Phe Ser Ser Cys Asp Val Pro Val Pro Leu His Leu Leu Gln
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- 5

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tgg ctg caa agc ttc ctg agg cct agg q
                                                                       419
Trp Leu Gln Ser Phe Leu Arg Pro Arg
         10
<210> 426
<211> 232
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 54..230
<221> sig_peptide
<222> 54..134
<223> Von Heijne matrix
      score 4.80000019073486
      seq VLLTSGVKPQTFA/VS
<400> 426
gcagtgagtg ttacagttct taaagatggt gtgtccggag tttgttcctt cca atg
                                                                        56
ttc aga tgt gtc cgg ttt ctt cct tct ggc ggg ttc gtg gtc ttg ctg
                                                                       104
Phe Arg Cys Val Arg Phe Leu Pro Ser Gly Gly Phe Val Val Leu Leu
                         -20
                                             -15
act tca gga gtg aag cca caa acc ttc gca gtg agt gtt aca gct ctt
                                                                       152
Thr Ser Gly Val Lys Pro Gln Thr Phe Ala Val Ser Val Thr Ala Leu
                     - 5
aaa ggt ggc atg ccc gga gtt gtt cat tcc tcc ggt ggg ttc gtg gtt
                                                                       200
Lys Gly Gly Met Pro Gly Val Val His Ser Ser Gly Gly Phe Val Val
ttg cta act tca gga gcg aas tgc aga cct tc
                                                                       232
Leu Leu Thr Ser Gly Ala Xaa Cys Arg Pro
<210> 427
<211> 383
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 226..381
<221> sig peptide
<222> 226..315
<223> Von Heijne matrix
      score 4.80000019073486
      seq CLFLNARLAGTLC/QL
<400> 427
acagacatca gctcgggtca accgcgggcc tcgagcccga gtggctgagg gctgttacct
                                                                        60
tcaaaccttt gaatcccacg ttttcccctt gacttcctgt caccgttaga gaaaagtgga
                                                                       120
cagcgtctcg gtcacagagt tggagaaata gtgcagggac tcttcaggga gagcgttttc
                                                                       180
ctcatcaaag caaactgcaa aatcgcttct gccggcgtgg acctg atg aga gtc ggt
                                                                       237
                                                  Met Arg Val Gly
                                                   -30
cgt cgt gag gga cac cct ctg ttc cct aac gtc ccc cgc tgc tta ttt
                                                                       285
Arg Arg Glu Gly His Pro Leu Phe Pro Asn Val Pro Arg Cys Leu Phe
                        -20
                                             -15
tta aac gct cgg ttg gcg gga acc ctg tgc cag ctg aaa ctc ctt cag
                                                                       333
Leu Asn Ala Arg Leu Ala Gly Thr Leu Cys Gln Leu Lys Leu Leu Gln
-10
                    - 5
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ttt ggc cgc cta gga aac acc gag agt cac cta cat ggg ctg gct ggg Phe Gly Arg Leu Gly Asn Thr Glu Ser His Leu His Gly Leu Ala Gly 10 15 20	381
99	383
<210> 428 <211> 132 <212> DNA <213> Homo sapiens	
<220> <221> CDS <222> 32130	
<221> sig_peptide <222> 32124 <223> Von Heijne matrix     score 4.80000019073486     seq LLCPLTCPHHSLS/TV	
<400> 428	
ttcaacaaat gagtcatagt gttttcgtat t atg tat ttt gat atc cag att Met Tyr Phe Asp Ile Gln Ile -30 -25	52
gtc tca gat gtg gtc agc ggg att ccc ttc aaa ctt ctg tgc cct tta Val Ser Asp Val Val Ser Gly Ile Pro Phe Lys Leu Leu Cys Pro Leu -20 -15 -10	100
aca tgt ccc cat cat tct ctg agc acc gtg gg Thr Cys Pro His His Ser Leu Ser Thr Val -5	132
<210> 429 <211> 165 <212> DNA <213> Homo sapiens	
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<221> CDS <222> 25165	·.
<221> sig_peptide <222> 25117	
<pre>&lt;223&gt; Von Heijne matrix score 4.80000019073486 seq FSPFLPSLPLLEA/ER</pre>	
<400> 429	
caaactgttg aaaagttaac tctt atg tta ttt ata ttt tca gac ata gat  Met Leu Phe Ile Phe Ser Asp Ile Asp  -30  -25	51
tgg aag atg gac tta tgc ttt ttc tct ttc tct cct tcc ctt ccc tcc  Trp Lys Met Asp Leu Cys Phe Phe Ser Phe Ser Pro Phe Leu Pro Ser  -20  -15  -10	99
ctt cct ttg ttg gag gct gaa aga atg agg gtc agt gat caa ctt cag Leu Pro Leu Leu Glu Ala Glu Arg Met Arg Val Ser Asp Gln Leu Gln	147
tat acc act gga kac ggg Tyr Thr Thr Gly Xaa Gly 15	165
<210> 430 <211> 236 <212> DNA	

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<213> Homo sapiens
<220>
<221> CDS
<222> 52..234
<221> sig peptide
<222> 52..159
<223> Von Heijne matrix
      score 4.80000019073486
      seg VLLAIGMFFTAWF/FV
<400> 430
gccgacgtgt tcttccggtg gcggasggcg gattagcctt cgcggggcaa a atg gag
                                                                        57
ctc gag gcc atg agc aga tat acc agc cca gtg aac cca gct gtc ttc
                                                                       105
Leu Glu Ala Met Ser Arg Tyr Thr Ser Pro Val Asn Pro Ala Val Phe
                                     -25
ccc cat ctg acc gtg gtg ctt ttg gcc att ggc atg ttc ttc acc gcc
                                                                       153
Pro His Leu Thr Val Val Leu Leu Ala Ile Gly Met Phe Phe Thr Ala
                                 -10
tgg ttc ttc gtt tac gag gtc acc tct acc aag tac act cgt gat atc
                                                                       201
Trp Phe Phe Val Tyr Glu Val Thr Ser Thr Lys Tyr Thr Arg Asp Ile
                        5
tat aaa gag ctc ctc atc tcc tta gtg gcc cga gg
                                                                      236
Tyr Lys Glu Leu Leu Ile Ser Leu Val Ala Arq
                    20
<210> 431
<211> 354
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 239..352
<221> sig_peptide
<222> 239..289
<223> Von Heijne matrix
      score 4 80000019073486
      seq LKLISTNFSLCQS/VQ
<221> misc_feature
<222> 345
<223> n=a, g, c or t
<400> 431
aggeettetg agtgeagetg geaccatggg tgtgeteeag ageaacttet gettgetetg
                                                                       60
agececetge cetgeeteec ettteaceat gttteetetg acaagatttt aagtacagea
                                                                      120
attcaagaag atttctcctc ctaaacgaca tttatctgaa gtctattgcc tcttgattgc
                                                                      180
tggaaaagad tcttaaaatc atttcaaaag taacttataa acaaacttat taaaagtg
                                                                      238
atg aaa gga gca ttg aaa tta att agc act aat ttt tca ctg tgc caa
                                                                      286
Met Lys Gly Ala Leu Lys Leu Ile Ser Thr Asn Phe Ser Leu Cys Gln
                            -10
agt gtg cag tgt cct tca gag gaa aca ata aca gat ctg gtg agt gtg
                                                                      334
Ser Val Gln Cys Pro Ser Glu Glu Thr Ile Thr Asp Leu Val Ser Val
                                        10
cca tgc cag tng gga ctg gg
                                                                      354
Pro Cys Gln Xaa Gly Leu
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20

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<210> 432
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 <212> DNA
 <213> Homo sapiens
 <220>
 <221> CDS
 <222> 153..431
 <221> sig_peptide
 <222> 153..359
 <223> Von Heijne matrix
       score 4.80000019073486
       seq MMVLSLGIILASA/SF
 <400> 432
gtaaaaaaac actggaataa ggaagggctg atgactttca gaagatgaag gtaagtagaa
                                                                        60
accepttgatg ggactgagaa accagagtta aaacctcttt ggagcttctg aggactcagc
                                                                       120
togaaccaac gggcacagtt ggcaacacca to atg aca toa caa cot gtt coo
                                                                       173
                                     Met Thr Ser Gln Pro Val Pro
aat gag acc atc ata gtg ctc cca tca aat gtc atc aac ttc tcc caa
                                                                       221
Asn Glu Thr Ile Ile Val Leu Pro Ser Asn Val Ile Asn Phe Ser Gln
                                                 -50
gca gag aaa ccc gaa ccc acc aac cag ggg cag gat agc ctg aag aaa
                                                                       269
Ala Glu Lys Pro Glu Pro Thr Asn Gln Gly Gln Asp Ser Leu Lys Lys
                         -40
                                             -35
cat cta cac gca gaa atc aaa gtt att ggg act atc cag atc ttg tgt
                                                                       317
His Leu His Ala Glu Ile Lys Val Ile Gly Thr Ile Gln Ile Leu Cys
                    -25.
ggc atg atg gta ttg agc ttg ggg atc att ttg gca tct gct tcc ttc
                                                                       365
Gly Met Met Val Leu Ser Leu Gly Ile Ile Leu Ala Ser Ala Ser Phe
                -10
                                     -5
tet eca aat tit acc caa gig act tet aca eig tig aac tet get tac
Ser Pro Asn Phe Thr Gln Val Thr Ser Thr Leu Leu Asn Ser Ala Tyr
                            10
                                                 15
cca ttc ata gga ccc ggg
                                                                       431
Pro Phe Ile Gly Pro Gly
    20
<210> 433
<211> 201
<212> DNA
<213> Homo sapiens
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<221> CDS
<222> 37..201
<221> sig peptide
<222> 37..156
<223> Von Heijne matrix
      score 4.80000019073486
      seq IVSAACKCGSSQA/AI
<400> 433
aatatttatg aagcagtttg gaaccaaagg ggtagt atg gta gac gag tgt ctt
                                                                       54
                                        Met Val Asp Glu Cys Leu
                                        -40
aca gag cct gtg tgg gga agc aaa agg caa ggg tgt agt tca cag gca
                                                                      102
Thr Glu Pro Val Trp Gly Ser Lys Arg Gln Gly Cys Ser Ser Gln Ala
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-25

gaa gcg agc tgt gac att gtc agt gca gcg tgt aag tgt ggc t Glu Ala Ser Cys Asp Ile Val Ser Ala Ala Cys Lys Cys Gly s -15 -10 -5	cc tca ' 150 Ser Ser
cag gcg gcc att gat tgt gag acc tca tct tgc tct gaa gat t Gln Ala Ala Ile Asp Cys Glu Thr Ser Ser Cys Ser Glu Asp I 1 5 10	ctc ccg 198 Phe Pro
gtg Val 15	201
<210> 434	
<211> 334	
<212> DNA <213> Homo sapiens	•
12137 Nomo Baptens	•
<220>	
<221> CDS	
<222> 242334	
<221> sig_peptide <222> 242283	· •
<223> Von Heijne matrix	
score 4 80000019073486 seq AWWFSGTFPLTHP/CS	.:
<400> 434	
aagetgtact ctttcagcac atttcctttc atctcccct tcttccctct tc	tgtgctct 60
caagactite eccetetige igecacagat geagigaage eigecatata ta igigiggeaa eteigeaggi ggggietaig caagetacag acceeteiga gi igecitagee iggeeiggai geciaceagg ecceaceae acciageige ig	aggtacaa 120 gtggtcag 180
a atg gca tgg tgg ttt tct gga acc ttc cca cta act cac ccc Met Ala Trp Trp Phe Ser Gly Thr Phe Pro Leu Thr His Pro -10	Cys Ser
gga tac ggc tct ctg atg gct cct tct agc cct acc cct tct gg	gg 334
Gly Tyr Gly Ser Leu Met Ala Pro Ser Ser Pro Thr Pro Ser G 5 10 15	ly
×210> 435	
<211> 386	
:212> DNA :213> Homo sapiens	
2137 Nomo Bupiens	
220>	
221> CDS 222> 152385	
222> 152365	
221> sig_peptide	
222> 152322	
223> Von Heijne matrix	
score 4.80000019073486 seq VTSLANLIPPVKA/TP	
400> 435	
gtcgagtcc tgcccggcta gaagccggct gtcggtctcc gtgtcgccgc cgc	egecegg 60
ategtggag ctggggeeec cttttgeetg ggagttttgt agtegeetag ggt	cagcoot 120
acateccaa agggeaggee eggeageege e atg gtg gee aag gat tac Met Val Ala Lys Asp Tyr -55	ccc 172 Pro
tc tac ctc acg gtc aag aga gcg aac tgc agc ctg gag cta cc he Tyr Leu Thr Val Lys Arg Ala Asn Cys Ser Leu Glu Leu Pr -40	O Pro -35
cc agc ggt ccg gcc aag gac gct gag gag cct agt aat aaa cg la Ser Gly Pro Ala Lys Asp Ala Glu Glu Pro Ser Asn Iws Ar	9 atc 268

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.-25
                -30
                                                         -20
aaa ccc ctt tcc cga gtc acg tcg cta gca aac ctc atc ccg ccc gtg
Lys Pro Leu Ser Arg Val Thr Ser Leu Ala Asn Leu Ile Pro Pro Val
                                -10
            -15
aag god acg coa tta aag ogd tto agt daa acc otg dag ogd tod att
Lys Ala Thr Pro Leu Lys Arg Phe Ser Gln Thr Leu Gln Arg Ser Ile
                                             10
age tto ege agt gag age gee t
                                                                       386
Ser Phe Arg Ser Glu Ser Ala
<210> 436
<211> 472
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 191..472
<221> sig peptide
<222> 191..274
<223> Von Heijne matrix
      score 4.80000019073486
      seq GVLLEPFVHQVGG/HS
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                                                                       60
gcgagcatcc tggccagaac aagccaagga gccaagacga gagggacaca cggacaaaca
                                                                      120
acagacagaa gacgtactgg ccgctggact ccgctgcctc ccccatctcc ccgccatctg
                                                                      180
cgcccggagg atg agc cca gcc ttc agg gcc atg gat gtg gag ccc cgc
                                                                      229
           Met Ser Pro Ala Phe Arg Ala Met Asp Val Glu Pro Arg
                       -25
gcc aaa ggc gtc ctt ctg gag ccc ttt gtc cac cag gtc ggg ggg cac
                                                                      277
Ala Lys Gly Val Leu Leu Glu Pro Phe Val His Gln Val Gly Gly His
-15
                    -10
tea tge gtg etc ege tte aat gag aca ace etg tge aag eec etg gte
                                                                       325
Ser Cys Val Leu Arg Phe Asn Glu Thr Thr Leu Cys Lys Pro Leu Val
cca agg gaa cat cag ttc tac gag acc ctc cct gct gag atg cgc aaa
                                                                      373
Pro Arg Glu His Gln Phe Tyr Glu Thr Leu Pro Ala Glu Met Arg Lys
        20
                            25
ttc act ccc Cag tac aaa gga Caa agc caa agg ccc ctt gtt agc tgg
                                                                      421
Phe Thr Pro Gln Tyr Lys Gly Gln Ser Gln Arg Pro Leu Val Ser Trp
                        40
cca tcc ctg ccc cat ttt ttc ccc tgg tcc ttt ccc ctg tgg cca cag
                                                                      469
Pro Ser Leu Pro His Phe Phe Pro Trp Ser Phe Pro Leu Trp Pro Gln
                                                                      472
gga
Gly
<210> 437
<211> 469
<212> DNA
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<222> 213..467
<221> sig_peptide
<222> 213..314
<223> Von Heijne matrix
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<210> 439 <211> 447 <212> DNA

<213> Homo sapiens

## score 4.80000019073486 seq ILAFLQSPRAILP/GN

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                                                                        60
cttttgcctt gcaggattct ttttcatctt tgcagggact tctggggccg gagtatgtaa
                                                                       120
aactcctggg tetetgtgtg tgcctgagtg getgetetae tgagaetetg catacacage
                                                                       180
tetgtatate ggacceawgg ecetggtgge atg ggc tea ega gga gat ece etg
                                  Met Gly Ser Arg Gly Asp Pro Leu
                                  -45
atc tgt ggg ttg caa aga tct gtg gga gaa gtg tgg ttt cct gga tgg
                                                                       282
Ile Cys Gly Leu Gln Arg Ser Val Gly Glu Val Trp Phe Pro Gly Trp
        -35
                            -30
                                                 -25
ggt cac aca atc act cac tgc ttc cct tgg ctg gag gtg ggg ctt ttt
                                                                       330
Gly His Thr Ile Thr His Cys Phe Pro Trp Leu Glu Val Gly Leu Phe
                         -15
                                             -10
ttt tgg ctc cat gct gct cct ggg cgg gcg att gcc cta ccc cat ttt
                                                                       378
Phe Trp Leu His Ala Ala Pro Gly Arg Ala Ile Ala Leu Pro His Phe
tct tca ttc tct gtg ggt caa gdb gtt cac ttg gtc agt cca ttg tgr
                                                                       426
Ser Ser Phe Ser Val Gly Gln Xaa Val His Leu Val Ser Pro Leu Xaa
            15
                                20
gam ctg gat att tca gtt gaa
                                                                      447
Xaa Leu Asp Ile Ser Val Glu
        30
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<221> sig peptide
<222> 176..232
<223> Von Heijne matrix
      score 4.69999980926514
      seg ELLLLPRGLCQV/CP
<221> misc feature
<222> 20,279..281
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agaaaagcag ccgcagttgn gccgctccac cacgccgtcc gggtgggcct agcagtcgct
                                                                       60
ccatttatcg cttgagatct ccagccttac cgcggctcga aatggacccc aactgctcct
                                                                      120
gcaccactgg tgtctccwrc gcctgcaccg gctcctgcac gtgcaaagag tgcaa atg
                                                                      178
cac ctc ctg caa gaa gag ctg ctg ctc ctg ctg ccc cgt ggg ctg tgc
                                                                      226
His Leu Leu Gln Glu Glu Leu Leu Leu Leu Pro Arg Gly Leu Cys
            -15
                                -10
caa gtg tgc cca cgg ctg tgt ctg caa agg gmc gtt gga gaa ctg cag
                                                                      274
Gln Val Cys Pro Arg Leu Cys Leu Gln Arg Xaa Val Gly Glu Leu Gln
```

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mtg cnn nky cct gat gtg gga aca gct ctt ctc cca gat gtt aat aga
                                                                       322
Xaa Xaa Xaa Pro Asp Val Gly Thr Ala Leu Leu Pro Asp Val Asn Arg
                     20
aca age tgc aca acc tgg
                                                                       340
Thr Ser Cys Thr Thr Trp
                 35
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<211> 409
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<221> sig_peptide
<222> 292..375
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       seq QLVTRLLLSPSQS/TQ
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agaagatggg gaaagaggaa ggaaaggatg cccagataca gggagcttta gcgatgtagt
                                                                       60
gaacggacag aagatcagga acaagttgag ttcattgtgt ggagatggca rraagatgga
                                                                       120
gattggtgag ctgagtggag aagtgccata gagcggtgtt ttgccagagt gtctgcggat
                                                                       180
tgctcatacc tgggaaggat tctttgtatg gttcccttag gctgagggag ggtatcagct
                                                                      240
ttacagacct tgtgggatta caaaagggcc accacact cttcaaccaa t atg tgt
                                                                      297
cta tot tgc att caa ggc tca ttc ttt gtt gaa att ttg cag ttg gtc
                                                                      345
Leu Ser Cys Ile Gln Gly Ser Phe Phe Val Glu Ile Leu Gln Leu Val
    -25
                        -20
act agg cta ttg tta tct cca tct caa agt aca cag aca cac aca cac
                                                                      393
Thr Arg Leu Leu Ser Pro Ser Gln Ser Thr Gln Thr His Thr His
                    -5
                                        1
aca cac aca cac aca a
                                                                      409
Thr His Thr His Thr
            10
<210> 442
<211> 320
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<221> CDS
<222> 203..319
<221> sig_peptide
<222> 203..298
<223> Von Heijne matrix
      score 4.69999980926514
      seq AILLLVXVSDKNE/QQ
<221> misc_feature
<222> 225..227,279
<223> n=a, g, c or t
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cacactagaa tagactggaa caacttggat ttagtgattc cgatgcttat caggaaggtc
tctgttcttt tataggaaga aaaaacatag ttattttct tttatgatac aaaggtatgc
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#TV	
tttctatgca agctggatac cagaccaaga ataataaatc acaatttcat aaggtttcta agacttgata ttatatgggg at atg acc att ttg agg gaa atg tnn nca tca Met Thr Ile Leu Arg Glu Met Xaa Xaa Ser -30	180 232
ctt tat gta ctt gaa gct aag gat act gct atc tta ttg ctt gtt tna Leu Tyr Val Leu Glu Ala Lys Asp Thr Ala Ile Leu Leu Leu Val Xaa -20 -15 -10	280
gtg agc gat aag aat gaa cag cag ctt ggg agg ggc gtg g Val Ser Asp Lys Asn Glu Gln Gln Leu Gly Arg Gly Val -5 1 5	320
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<222> 102254	
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gtagctcacc atggttttaa tttgcatttc tctgataatg a atg aga ctt agt tct Met Arg Leu Ser Ser -25	116
tcc tgt ggg ttg cct gtt aag act ttg cca ttt atc tgt tgc aat ctt Ser Cys Gly Leu Pro Val Lys Thr Leu Pro Phe Ile Cys Cys Asn Leu -20 -15 -10	164
tat ttc ttg ctg ttt tgt agg agt tct ttt tta tat ttt gga tat gat Tyr Phe Leu Phe Cys Arg Ser Ser Phe Leu Tyr Phe Gly Tyr Asp -5	212
ccc att aat act tac atg tat tac aat gtt ttc tcc cac tcg gg Pro Ile Asn Thr Tyr Met Tyr Tyr Asn Val Phe Ser His Ser 10 15 20	256
<210> 444	
<211> 284 <212> DNA <213> Homo sapiens	
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tagatggcga ctccct atg tta ctg acg aga ccg gcg gtg agt gcg gga ggc Met Leu Leu Thr Arg Pro Ala Val Ser Ala Gly Gly -65 -60	52
gcg gas cgc ttc tct ccg ggc tct cgg ggc agg ggt tcg gac ttg gaa Ala Xaa Arg Phe Ser Pro Gly Ser Arg Gly Arg Gly Ser Asp Leu Glu	100

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agg ggt ctg tgc ccc gcc cat ccc ggg gcc cct cct ttg ccc cgc ccc
 Arg Gly Leu Cys Pro Ala His Pro Gly Ala Pro Pro Leu Pro Arg Pro
                     -35
                                        -30
 ccg gac cgc ctt ccc cat tca ttc tct cct acg ggg tgt ctc ctg hgc
                                                                    196
 Pro Asp Arg Leu Pro His Ser Phe Ser Pro Thr Gly Cys Leu Leu Xaa
                -20
                                    -15
 ecc ett etg gte teg tgt ttg ggg tet etg ett eeg gte acc caa acc
                                                                    244
 Pro Leu Leu Val Ser Cys Leu Gly Ser Leu Leu Pro Val Thr Gln Thr
             - 5
ctg ggg tcc ttc agt gct ggt ccc tgc ttc agg acc ctc a
                                                                    284
Leu Gly Ser Phe Ser Ala Gly Pro Cys Phe Arg Thr Leu
                        15
<210> 445
<211> 240
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<213> Homo sapiens
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<222> 103..240
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<222> 103..177
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tettttgtaa tgaageatgg cagecaggee tageacaett eeetetgeac accateetge
                                                                     60
tcaggcctct gtgcctcggc tgtgctgttc cttctgcttg ga atg cat tca ctg
                                                                    114
                                              Met His Ser Leu
                                              -25
tgt cca ctt agc caa ttc cta cct att ctt tma agc ctc agt tcc agt
                                                                    162
Cys Pro Leu Ser Gln Phe Leu Pro Ile Leu Xaa Ser Leu Ser Ser Ser
                       -15
                                           -10
gtc ccc tcg agg gca ggc agt gct ttc cca tct gcc cta ggt cca ctc
                                                                    210
Val Pro Ser Arg Ala Gly Ser Ala Phe Pro Ser Ala Leu Gly Pro Leu
tac cag cct cta ctt ggg ccc cca gca tgg
                                                                    240
Tyr Gln Pro Leu Leu Gly Pro Pro Ala Trp
           15
<210> 446
<211> 184
<212> DNA
<213> Homo sapiens
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<221> sig_peptide
<222> .8...139
<223> Von Heijne matrix
     score 4.69999980926514
     seq LVFLSVXLLFLLF/LV
Met Arg Thr Gln Val Tyr Glu Gly Leu Cys Lys Asn Tyr Phe
                       -40
                                           -35
tet ett get gta eta caa aga gat aga ate aaa etg ett ttt tte gae
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<221> CDS <222> 39..122 <221> sig\_peptide

<222> 3992 <223> Von Heijne matrix score 4.69999980926514 seq IAILFPNSGSCFA/FS	•
<400> 448 cttatctgat tcacagcccg tattcagatt tgccaatt atg ttg att ttc att att Met Leu Ile Phe Ile Ile	56
gct att tta ttt ccc aat tca gga tca tgc ttt gca ttt agt tgt cat Ala Ile Leu Phe Pro Asn Ser Gly Ser Cys Phe Ala Phe Ser Cys His -10 -5 1	104
gtc tcc ttt ttt ttt t Val Ser Phe Phe Phe 5 10	123
<210> 449 <211> 193 <212> DNA <213> Homo sapiens	
<220> <221> CDS <222> 18191	
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<pre>&lt;400&gt; 449 ctctctcctg ttcggtc atg gtg aga tgt gct tgc ttc ccc ttc ttc ccc</pre>	50
ttc gcc ttc tgc cat gac tgt aag ttt ctt ggg gcc tcc cag tca tgc Phe Ala Phe Cys His Asp Cys Lys Phe Leu Gly Ala Ser Gln Ser Cys 1 5 10	98
ttc ttg tta agc cgg caa aac tgt gta agc aca gga kga cct tca tcc Phe Leu Leu Ser Arg Gln Asn Cys Val Ser Thr Gly Xaa Pro Ser Ser 15 20 25	146
aaa tot gat ato aac toa agg tot gga tot tgt toa otg goa agg gg Lys Ser Asp Ile Asn Ser Arg Ser Gly Ser Cys Ser Leu Ala Arg 30 35 40	193
<210> 450 <211> 302 <212> DNA <213> Homo sapiens	
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<222> 292 <223> n=a, g, c or t

<400> 450 ccagcaa atg gtg agt ttg agg gta ggg gcc tct cca ttt cgg ttc cca ' Met Val Ser Leu Arg Val Gly Ala Ser Pro Phe Arg Phe Pro -25 ctg gcc ccc ctc tbt ttg gtt ttc atc tct ctt ctc cca gcc cca ttt 97 Leu Ala Pro Leu Xaa Leu Val Phe Ile Ser Leu Leu Pro Ala Pro Phe -10 ttt cct act ctt tcg ttt cct tgt tgc tgt gtg tcc tgg ctc ttt tct 145 Phe Pro Thr Leu Ser Phe Pro Cys Cys Cys Val Ser Trp Leu Phe Ser ctt tet gtg vtt gtc tet etg egt etc agt ett tbt gtg tee tgt tta 193 Leu Ser Val Xaa Val Ser Leu Arg Leu Ser Leu Xaa Val Ser Cys Leu 30 tet etc tgg tgt etc ttg gta ttg ttt etc tet ecc act etg tat gte 241 Ser Leu Trp Cys Leu Leu Val Leu Phe Leu Ser Pro Thr Leu Tyr Val 50 tet gae tea tte tge tea tte tgt gte ete eet att get ete tgt eee 289 Ser Asp Ser Phe Cys Ser Phe Cys Val Leu Pro Ile Ala Leu Cys Pro 60 can gct cgt tct t 302 Xaa Ala Arg Ser 70 <210> 451 <211> 367 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 150..365 <221> sig\_peptide <222> 150..311 <223> Von Heijne matrix score 4.69999980926514 seq PGLAFLAILTVLA/KP <400> 451 aaaatgatcc atgcacacag cctctatagg aaagaaaaaa aatatccaat tgattttctt 60 cccttttctg cttctaaagt ataccaaatt tcactgtgat cttaatattc cccagaacag 120 acacctetga geagagagea ggeettaga atg gee cae eee tgt tta get eea 173 Met Ala His Pro Cys Leu Ala Pro gca gaa cct tct act ctt tca caa acc kcc cat cca att caa aga acc 221 Ala Glu Pro Ser Thr Leu Ser Gln Thr Xaa His Pro Ile Gln Arg Thr -40 ctg aca act ttc cct cag gct tgg gtt cta acc agc agc ttt tcc ata 269 Leu Thr Thr Phe Pro Gln Ala Trp Val Leu Thr Ser Ser Phe Ser Ile -25 -20 cag cca ggc ctt gca ttc cta gcc att ctc acc gtg tta gcc aaa ccc 317 Gln Pro Gly Leu Ala Phe Leu Ala Ile Leu Thr Val Leu Ala Lys Pro -10 ggs tcc tct amc tgg agt cct ggt cag ttc aca cca cac tcc ctg ctg 365 Gly Ser Ser Xaa Trp Ser Pro Gly Gln Phe Thr Pro His Ser Leu Leu 99 367

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<222> 244..348
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aagaaattgc cagtcaagcc agccaggtag gttaaatcta tcctggcagt cctggagact
gctgcagact gactgcctga tgtccgtgcc cactggggtt tttccctttt cagaaaggat
ttctccctga tctctcccca caaactctgg ctttgctttt tcatttccta agagcaactc
                                                                      240
aat atg cat ttc ccc atc caa gct acc ttc sac tat tcc cct act gat
    Met His Phe Pro Ile Gln Ala Thr Phe Xaa Tyr Ser Pro Thr Asp
                             -25
                                                 -20
tet etc tgt cat tta tat ttk tea etc tte tet tee ttt etc tge tet
                                                                      336
Ser Leu Cys His Leu Tyr Xaa Ser Leu Phe Ser Ser Phe Leu Cys Ser
    -15
                         -10
acc cct gcc cgg g
                                                                      349
Thr Pro Ala Arg
<210> 453
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                                                                       60
gggattccaa tccaagctct gggcca atg gct ttg cat atc cta gaa tgc gag
                                                                      113
                             Met Ala Leu His Ile Leu Glu Cys Glu
                                 -35
agg aac gtt tgt ttt gta gca gtt aga cag cct gct cat gaa agc tgc
                                                                      161
Arg Asn Val Cys Phe Val Ala Val Arg Gln Pro Ala His Glu Ser Cys
        -25
                            -20
ttt gtg ccc agc ctt gtg aca ggt gct tta caa caa tcc cag aca cag
                                                                      209
Phe Val Pro Ser Leu Val Thr Gly Ala Leu Gln Gln Ser Gln Thr Gln
                        -5
cac cca cct tgg gtt tgc cct cag gta cag ggc tcc tat cca tcc tgg
                                                                      257
His Pro Pro Trp Val Cys Pro Gln Val Gln Gly Ser Tyr Pro Ser Trp
                                    15
aag aac aga ggg a
                                                                     270
Lys Asn Arg Gly
           25
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WO 99/53051 PCT/1B99/00712 246 <211> 492 <212> DNA <213> Homo sapiens <220> <221> CDS

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<222> 317..490

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60

177

ttt tct gta cac aga gag tac cgt gtc ctc mta ctg tgt aac agt agg 400 Phe Ser Val His Arg Glu Tyr Arg Val Leu Xaa Leu Cys Asn Ser Arg -15 -10 qtc tct ttc act cgn ntc cat gtg aag aga cca cca wac agg cta tgt 448 Val Ser Phe Thr Arg Xaa His Val Lys Arg Pro Pro Xaa Arg Leu Cys

gtg agc agc aaa ggc tgt tta ttt cac ctg ggt gca ggc agg ct 492 Val Ser Ser Lys Gly Cys Leu Phe His Leu Gly Ala Gly Arg 20

<210> 455 <211> 177

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<222> 56..112

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<400> 455

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cag gtg ttg ttt tgt aat cga ag

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Gln Val Leu Phe Cys Asn Arg
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ctaattgaaa agg atg tcc tat ttc cga tgt ata ttt ttg gca gtt ttg
                                                                        49
                Met Ser Tyr Phe Arg Cys Ile Phe Leu Ala Val Leu 🕠
                            -15
                                                -10
tca aaa atc agt tgg gct gta aat atg tgc agt ctt att tct ggg tcc
                                                                        97
Ser Lys Ile Ser Trp Ala Val Asn Met Cys Ser Leu Ile Ser Gly Ser
    - 5
                         1
tcg gg
                                                                       102
Ser
<210> 457
<211> 151
<212> DNA
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<220>
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<222> 35..151
<221> sig_peptide
<222> 35..136
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      seq LFLSISLITLYYS/SE
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                                                                       55
                                      Met Leu Cys Ile Met Phe Gly
att gaa act aat gaa att acc aag atg aca atg tot ttt ctt ttg ttt
                                                                      103
Ile Glu Thr Asn Glu Ile Thr Lys Met Thr Met Ser Phe Leu Leu Phe
        -25
                            -20
                                                 -15
cta agt atc agt ttg ata act tta tat tcc tca gaa gca tgt ggg
                                                                      151
Leu Ser Ile Ser Leu Ile Thr Leu Tyr Tyr Ser Ser Glu Ala Cys Gly
    -10
                        -5
                                            1
<210> 458
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290

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caa gtg cca aca tac ggc cct tac ggc cgc tgt gcc ccc atg aag agc

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                                                                       120
taagaaaaaa gctctaagca cgcagggtag ccagacagac atg gat atg aga tgg
                                                                       175
                                             Met Asp Met Arg Trp
cac tgt gaa aac tcg cag acc aca gat gac atc ctt gtg gcc tca gca
                                                                      223
His Cys Glu Asn Ser Gln Thr Thr Asp Asp Ile Leu Val Ala Ser Ala
    -80
                        -75
                                             -70
gag tgt ccc agc gat gat gag gac att gac ccc tgt gag ccg agc tca
                                                                      271
Glu Cys Pro Ser Asp Asp Glu Asp Ile Asp Pro Cys Glu Pro Ser Ser
                    -60
                                         -55
ggt ggg tta gcc aac cca acc cga gca ggc ggc aga gag ccg tat cca
                                                                      319
Gly Gly Leu Ala Asn Pro Thr Arg Ala Gly Gly Arg Glu Pro Tyr Pro
                                    -40
                                                         -35
ggc tca gca gaa gtg atc cgg gag tcc agc agc acc acg ggt atg gtc
                                                                      367
Gly Ser Ala Glu Val Ile Arg Glu Ser Ser Ser Thr Thr Gly Met Val
            -30
                                -25
                                                     -20
gtt ggg ata gta gcc gcc gcc ctg tgc atc ctt atc ctc ctc wat
                                                                      415
Val Gly Ile Val Ala Ala Ala Leu Cys Ile Leu Ile Leu Leu Xaa
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                            -10
gcc atg tac a
                                                                      425
Ala Met Tyr
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tct Ser 1	gac	ctg Leu	act Thr	cag Gln 5	gac Asp	cct Pro	gct Ala	gtg Val	Ser 10	gtg Val	gcc	ttg Leu	gga Gly	cag Gln 15	aga Arg	,	, 152
gtc Val	agg Arg	atc Ile	aca Thr 20	tgc Cys	cag Gln	gga Gly	gac Asp	aac Asn 25	ctc Leu	gaa Glu	gag Glu	tat Tyr	ttt Phe 30	gca Ala	agc Ser		200
Trp	Tyr	35	Gln	Arg	Pro	Gly	Gln 40	Ala	Pro	Val	Leu	Val 45	Ile	Tyr	Gly		248
Lys	Asn 50	aac Asn	Arg	Pro	Ser	Gly 55	Ile	Pro	Xaa	Arg	Xaa 60	Ser	Gly	Ser	Lys		296
Ser 65	Gly	aat Asn	Thr	Ala	Leu 70	Leu	Thr	Ile	Xaa	Gly 75	Ala	Gln	Ala	Glu	Asp 08	,	344
Xaa	Ala		Tyr	Tyr 85	Cys.	Ser	Xaa	Arg	Asp 90	cat His	act Thr	gat	aat Asn	cgg Arg 95	tgg Trp	'	392
		ggc Gly					_		g								420
<211 <212	)> 46 .> 25 !> DN !> Ho	57	apie	ns													
	> CI	os 525	5		,				·			V					
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ttt Phe	tac Tyr -15	atg Met	gkg Xaa	att ( Ile )	Leu '	acc Thr	tgc Cys	ttg Leu	atc Ile	ttc Phe	agg Arg -5	aac	tca	gaa Glu	9 <b>9</b> 9 Gly		105
ttt Phe 1	cag	att Ile	Xaa :	cat q His '	gtc Val	cag Gln	aaa Lys	caa Gln	cag Gln 10	tgt Cys	ctt	ttc Phe	aaa Lys	aat Asn 15	gag Glu		153
aaa Lys	gtg Val	gtc Val	gtg ( Val ( 20	ggc ( Gly s	ca Ser (	tgc ( Cys (	aac Asn	agg Arg 25	acc Thr	atc Ile	cag Gln	aac Asn	cag Gln 30	cag	tgg Trp		201
		act ( Thr (				Lys :					Lys						249
Leu	gcc Ala 50	at															257

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 atg tgc gtg tgc gcg tgt gct ttg tgt gtg tgg ttg tgt gtt aaa tca
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 Met Cys Val Cys Ala Cys Ala Leu Cys Val Trp Leu Cys Val Lys Ser
         -15
 tgc agt att
                                                                        117
 Cys Ser Ile
    1
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                                           Met Ile Ser Asp Val Gln
                                               -20
cac ctt ttc ata tac ttg tta gcc ttt tgt atg cct tcc ttg gag aaa
                                                                       104
His Leu Phe Ile Tyr Leu Leu Ala Phe Cys Met Pro Ser Leu Glu Lys
-15
                    -10
                                         -5
tgt cta tac ggg tct ttg gcc cac ttt ttt ttt ttt tt.
                                                                       142
Cys Leu Tyr Gly Ser Leu Ala His Phe Phe Phe
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                                                                       120
aacttgagtg gctgcttttc tgggtggaaa agagcggtat cagacagggt gagcagtcgg,
                                                                       180
 ggaacggatg aacaaagact tgcaccgtgg ccctg atg cct ttg ttc cga gtt
                                                                       233
                                        Met Pro Leu Phe Arg Val
cta ttc agt tgw act tgt gcg ttg twa cag gac ttt aga atg cag ccc
                                                                       281
Leu Phe Ser Xaa Thr Cys Ala Leu Xaa Gln Asp Phe Arg Met Gln Pro
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tgc ccc cca acc ccc aag g
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Cys Pro Pro Thr Pro Lys
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                                                                       120
atgcattete agaaagatee tatee atg tgg tat gta gag atg tgg gtt tet
                                                                       172
                            Met Trp Tyr Val Glu Met Trp Val Ser
                                             -20
ttt ttt cta ctt ttt tat gtg ctt ctt ttt aga aac tta tac aca cac
                                                                       220
Phe Phe Leu Leu Phe Tyr Val Leu Leu Phe Arg Asn Leu Tyr Thr His
aca cac cac act ggg
                                                                       235
Thr His His Thr Gly
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PCT/IB99/00712

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 atactetget ettgttaggt tetagaaatg teaattacet caaattetet gagagtgeag
                                                                       180
 ctcagttctt ctatatcctt actggtttct gcctacttgc tctgtcagtt actgagcaaa
                                                                       240
 aagtagcaaa gtctgcagct gtaatacatt tgtttatttc tctcattttt gttagtattt
                                                                       300
gcttcatgta ctttgaagct rtgttgttag catgcataca cataggatga ttatggcttc
                                                                       360
ttggaaaatt gaccccttta gcattatgta atg ttc ctc ttt ttc ttt ggt aac
                                  Met Phe Leu Phe Phe Gly Asn
agt cca tgt tgt gga gcc aca ggg
                                                                       438
Ser Pro Cys Cys Gly Ala Thr Gly
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                               -20
                                                    -15
ctc tet etc tet etc teg gee tec etc att att tet ecc tet ecc tec
                                                                       97
Leu Ser Leu Ser Leu Ser Ala Ser Leu Ile Ile Ser Pro Ser Pro Ser
        -10
                            -5
gcc tct cca tct ctc ctt sct ccc cct bcc cgg g
                                                                     . 131
Ala Ser Pro Ser Leu Leu Xaa Pro Pro Xaa Arg
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ttt gtg ttt tta gta ggc acg ccg tgt ctc tcc atg ttg ctc agg ctg Phe Val Phe Leu Val Gly Thr Pro Cys Leu Ser Met Leu Leu Arg Leu -20 -15 -10	165
gtc tcc aac tcc cga cct cct gtg atg cgc cca cct cgg cct ggg g Val Ser Asn Ser Arg Pro Pro Val Met Arg Pro Pro Arg Pro Gly -5 1 5	211
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att cgg tta tta tta cta tat tta cag aat cct gta acc atc aca att  Ile Arg Leu Leu Leu Tyr Leu Gln Asn Pro Val Thr Ile Thr Ile  -20  -15 -10	99
tta ttt tta atc gtt tcc atg gcc ctg aaa ata aac cac ata ccc aag Leu Phe Leu Ile Val Ser Met Ala Leu Lys Ile Asn His Ile Pro Lys -5 1 5	147
999 Gly	150
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aaaatgctat aatccaaaca cctgtttgga ctcaatatgt catttt atg tct tgt  Met Ser Cys	180 235
atg tca ctt ttc ccc tgt tgc cct gct cag agt aag aat tat atg tta  Met Ser Leu Phe Pro Cys Cys Pro Ala Gln Ser Lys Asn Tyr Met Leu -10 -5 1 5	283
tta tta ttc att att tta ctt cca act caa ttt tta tat tca aaa tta	331

£50	
Leu Leu Phe Ile Ile Leu Leu Pro Thr Gln Phe Leu Tyr Ser Lys Leu 10 15 20	•
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ta caa gag aga tot oto ttt gag ama aag aga ggo got oot ooa agt Leu Gln Glu Arg Ser Leu Phe Glu Xaa Lys Arg Gly Ala Pro Pro Ser -45 -40 -35	160
gc aat att gaa gac ttc cat gga ctc tta ccg aag gtt atc ccc atc Ger Asn Ile Glu Asp Phe His Gly Leu Leu Pro Lys Val Ile Pro Ile 30 -25 -20 -15	208
gt gct cta tat gtg att tgc cag ttc att cta ata agg agt gga gtc	256

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-20

- 5

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-15

1

216

-25

-10

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60 120

gtagtaggga a gtgatgggag o	aaagtgtcag ccc cctctaaatg act	gagattt a atg	ctaag taccaccca tct act acc ta Ser Thr Thr Ty -55	t ttg aat 232
Glu Asp Leu -50	Lys Lys Lys P -45	he Ser Ala Va	k ata gag cag g l Ile Glu Gln V -40	al Leu Phe -35
Ala His Leu	Ser Pro Leu H	is Val Trp Let -2!		er Leu Cys
Glu Xaa Leu	Thr Cys Ile T	rp Val Arg Phe -10		la Ser Ser 5
caa gca tgc Gln Ala Cys 1	tcc aaa tgc a Ser Lys Cys A	ac tee teg tit sn Ser Ser Phe	ctc atc atg t Leu Ile Met S 10	ca tcc tct 424 er Ser Ser
tca cc Ser 15				429
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tctttgcaca tt	tgacttcta tggt	gcctac aacacg atg gca ctt	tcag tgttggtgaa tcag cttgtggaat atc gtt cta cag	tgagctgctt 120 g cta aca 171
			Ile Val Leu Glr -35	
Phe Gly Ile C	Gly Tyr Val Th -25	r Leu Leu Gln	att cat tcc at Ile His Ser Il -20	e Tyr Ser -15
Gln Leu Ile I	lle Leu Asp Le -10	u Leu Val Pro -5	gta ata ggc tt Val Ile Gly Le	eu Ile Thr 1
Glu Leu Pro I 5	Leu His Ile Ar	Glu Thr Leu 10	ctg ttt act to Leu Phe Thr Se 15	r Ser Leu
att ctc aca t Ile Leu Thr I 20	ta aat aca gt Leu Asn Thr Va 25	ttt gtc ctg Phe Val Leu	gca gtg aaa ct Ala Val Lys Le 30	g aar tgg. 363 u Lys Trp
	cc aca cga ta Ser Thr Arg Ty: 40	_		385
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                                           Met Arg Val Ala Gly Ala
gca aar ttg gtg gta rct gtg gca rtg ttt tta ctg aca ttt tat gtt
                                                                       104
Ala Lys Leu Val Val Xaa Val Ala Xaa Phe Leu Leu Thr Phe Tyr Val
             -15
                                -10
att tot caa gta ttt gaa ata aaa atg gat gca agt tta gga aat cta
                                                                       152
Ile Ser Gln Val Phe Glu Ile Lys Met Asp Ala Ser Leu Gly Asn Leu
                                             10
ttt gca aga tca gca ttg gac aca gct gca cgt tct aca aag cct ccg ,
                                                                      200
Phe Ala Arg Ser Ala Leu Asp Thr Ala Ala Arg Ser Thr Lys Pro Pro
gg
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gcggggctgg aggcggtggc tgcggttgcg ggaccggcac tatgctgggc cttcctacca
                                                                       60
cttatgtgtg gcttggtagt ggcctagggt ctctcctcc tgctgaagtc cctctcctgc
                                                                      120
aggtggccgt ctgcccggcc cagcacc atg cac acg ctt gtg ttc ttg agc aca
                                                                      174
                              Met His Thr Leu Val Phe Leu Ser Thr
                                                  -10
cgg cag gtg ctg cag tgc cag cca gct gcc tgc cag gcc ctg ccc ctg.
                                                                      222
Arg Gln Val Leu Gln Cys Gln Pro Ala Ala Cys Gln Ala Leu Pro Leu
ctg cca cgc gaa ctc ttc ccc ctg ctg ttc aag gtg gcc ttc atg ghc
                                                                      270
Leu Pro Arg Glu Leu Phe Pro Leu Leu Phe Lys Val Ala Phe Met Xaa
                                    20
aag aag aca gtg gta ctg cgc gak ttg gta cac acg cgg g
                                                                      310
Lys Lys Thr Val Val Leu Arg Xaa Leu Val His Thr Arg
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                                                                         60
 attotgacgg taactgtgta toagttggaa ttactgoact aactttgagg gooatactoa
                                                                        120
 aggactecaa taataaccaa gtcaatggee ttagtggaaa tacaacaatt cegtttagca
                                                                       180
 gctgttgggc caactacaca gaccttactc cccttagaac aggaaaaaat tataagattg
                                                                        240
 aatttatact ggataatgtt gttggggtag aatccagaac tttcagcctg ctggcagagt
                                                                        300
 ctgtctctag cagtggcagc agcagcagca gcmacagcaa agcatcaact gtgggtacat
                                                                        360
 atgcccagat a atg act gtm gta att agc tgt ctg gtt gga gaa tgt ggc
              Met Thr Val Val Ile Ser Cys Leu Val Gly Glu Cys Gly
                              -10
 tct tgg aaa t
                                                                        420
 Ser Trp Lys
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      score 4.5
      seq PIFGLLVPSQIFS/SL
caaccatac atg tgc aca ctc aca gac aca cac act cac gtc caa gtg cac
                                                                        51
          Met Cys Thr Leu Thr Asp Thr His Thr His Val Gln Val His
                   -45
                                       -40
aag tca aaa cct tgc cag ctc ctc tcc cct cct cca cca rsc cat ggt
                                                                        99
Lys Ser Lys Pro Cys Gln Leu Leu Ser Pro Pro Pro Pro Xaa His Gly
                                 -25
eet ett ett etc eet ate tit gge ett ett gig eec tet eag att tic
                                                                       147
Pro Leu Leu Pro Ile Phe Gly Leu Leu Val Pro Ser Gln Ile Phe
        -15
                             -10
                                                 -5
age tet ett ete aat tet eta eat etg gge etg eet tee tte eea aag
                                                                       195
Ser Ser Leu Leu Asn Ser Leu His Leu Gly Leu Pro Ser Phe Pro Lys
                                        10
                                                             15
atg cca ctc atg att ttc ctc ccc cgc tgg g
                                                                       226
Met Pro Leu Met Ile Phe Leu Pro Arg Trp
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<222> 221..409

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tqtagtcgtg catcettete accetecgtt agaaageete eteteateet cagaagaeta
                                                                       120
ctgtcagagg atgtaggvat ggacatecee tttgaagagg gegtgetgag teceagtget
                                                                       180
gcagacatga ggcctgaacc tcctaattct ctggatctta atg aca ctc atc ctc
                                                                       235
                                            Met Thr Leu Ile Leu
gga gaa tca agc tca cag ccc caa ata tca atc ttt ctc tgg acc aaa
                                                                       283
Gly Glu Ser Ser Ser Gln Pro Gln Ile Ser Ile Phe Leu Trp Thr Lys
             -55
                                 -50
gtg aag gat cta ttc tct ctg atg ata act tgg aca gtc cag atg aaa
                                                                      331
Val Lys Asp Leu Phe Ser Leu Met Ile Thr Trp Thr Val Gln Met Lys
                            -35
ttg aca tca atg tgg atg aac ttg ata ccc ccg atg aag cag att ctt
                                                                      379
Leu Thr Ser Met Trp Met Asn Leu Ile Pro Pro Met Lys Gln Ile Leu ,
                        -20
                                             ~15
tdg agt aca ctg gcc atg aag atc cac agc caa caa aga ttc tgg cca
                                                                       427
Xaa Ser Thr Leu Ala Met Lys Ile His Ser Gln Gln Arg Phe Trp Pro
                     -5
aga qtc aga gtc tat tcc aga ata tac
                                                                       454
Arg Val Arg Val Tyr Ser Arg Ile Tyr
            10
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<221> CDS
<222> 253..327
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                                                                       60
ctcctttttg ggtccatatt aattttaaaa cagttttttc tggttttgtg aaggatgtca
                                                                      120
ttggtagttt ataggaatag cahtgaatct gtagattgct ttgggcagta tggccatttt
                                                                      180
aacaatatta attetteeta tetatgaata tggaatgttt tteeatgtgt ttgtgteate
                                                                      240
tetttatace tg atg tat aaa gaa aag etg gta tta tte eta etc aat etg
                                                                      291
              Met Tyr Lys Glu Lys Leu Val Leu Phe Leu Leu Asn Leu
                              -15
ttc caa aaa att gag gag gag gaa ctc ttc cct aat ga
                                                                      329
Phe Gln Lys Ile Glu Glu Glu Leu Phe Pro Asn
    -5
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<222> 149..412
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       seq LELVATLPDDVQP/GP
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 <223> n=a, g, c or t
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gaaagtgcag gcagctgtgg aaggcgaagt tcaatcccag agtccgccc ctgaattggg
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gcctttccgg aggaggaagc tctgaaaaac aggggggccc agtgccattc cgcagggaat
                                                                       120
 tgtcgcttgc gttcagctgt tctacaca atg gac tca gta cct gcc act gtg
                                                                       172
                                Met Asp Ser Val Pro Ala Thr Val
cct tct atc gcc gct acc ccg ggg gac ccg gaa ctt gtg gga ccc ttg
                                                                       220
Pro Ser Ile Ala Ala Thr Pro Gly Asp Pro Glu Leu Val Gly Pro Leu
                     -35
                                         ~30
tet gtg etc tac gea gee tte ata gee aag etg etg gag eta gtt get
                                                                       268
Ser Val Leu Tyr Ala Ala Phe Ile Ala Lys Leu Leu Glu Leu Val Ala
                 -20
                                     -15
aca ttg cct gat gat gtt cag cct ggg cct gat ttt tat ggr stg sca
                                                                       316
Thr Leu Pro Asp Asp Val Gln Pro Gly Pro Asp Phe Tyr Gly Xaa Xaa
tgg aaa ctg tat tta tca ctg cct tct tgg gaa tkg ttc gtt tgc cat
                                                                       364
Trp Lys Leu Tyr Leu Ser Leu Pro Ser Trp Glu Xaa Phe Val Cys His
    10
                        15
                                             20
ttt ctt atg gag act gtc ctt gtt gtg aag gnt aga gta tat cwa gtc
Phe Leu Met Glu Thr Val Leu Val Val Lys Xaa Arg Val Tyr Xaa Val
25
                    30
ac
                                                                       414
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      seq AVWASVASPASIC/CG
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                                                                       60
gatetece atg gee geg tat the gee gta tgg gee teg gte geg agt eee
                                                                      110
         Met Ala Ala Tyr Phe Ala Val Trp Ala Ser Val Ala Ser Pro
                     -15
gca tcc atc tgt tgc ggr amy tgg ctc aca ggg ctg gtg cgg cac gaa
                                                                      158
Ala Ser Ile Cys Cys Gly Xaa Trp Leu Thr Gly Leu Val Arg His Glu
cgc atc gag gca cca tgg gcg cgt ggg
                                                                      185
Arg Ile Glu Ala Pro Trp Ala Arg Gly
        15
                            20
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                                                                        60
ctataatttg tatctaaaat taggttttcc cttttaagtt gttaattttc tatggkttgt
                                                                       120
gctgcatgct ttcactttta ttagtactta cagccaaaga gatgggcaaa tgtctagaaa
                                                                       180
aattaatgtt ttgattcagg aatttgtgcc tagtgatggc ctccaataga gaattttcca
                                                                       240
gagaga atg aag act cag ttt cta agt tgg ggc aaa ttt agt ttt tgt
                                                                       288
       Met Lys Thr Gln Phe Leu Ser Trp Gly Lys Phe Ser Phe Cys
                        -25
ttt ggt att ctt ctt ata tta cag cta tta aaa bnn tct ctt aaa aaa
                                                                       336
Phe Gly Ile Leu Leu Ile Leu Gln Leu Leu Lys Xaa Ser Leu Lys Lys
                     -10
                                         -5
tgc cgg' cac ggg
                                                                       348
Cys Arg His Gly
<210> 492
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      seq LRFILPSSWDCRC/AP
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ctac atg ctt cct gct gtg gct gtc tcg gaa ccc gtg gtc ctc cgc ttc
                                                                       49
     Met Leu Pro Ala Val Ala Val Ser Glu Pro Val Val Leu Arg Phe
                         -20
att ctg ccg agt tcc tgg gat tgc agg tgc gcg ccg cca ctc ctg act
                                                                       97
Ile Leu Pro Ser Ser Trp Asp Cys Arg Cys Ala Pro Pro Leu Leu Thr
-10
                    - 5
ggt ttt tgt att ttt tgg ktg gag acg gg
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Gly Phe Cys Ile Phe Trp Xaa Glu Thr
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ccgggctatc ccagtggctt caggcacctt ctccagacct acccagaaag atgcccgg
                                                                       118
atg gat cct gca gct ccg tgg ctt ttc tgg gaa gca gcg gcc cct gct
                                                                       166
Met Asp Pro Ala Ala Pro Trp Leu Phe Trp Glu Ala Ala Ala Pro Ala
             -30
                                 -25
ctc aag aga ccc tgg ctc ctg atg gtg gcc cca agg ttg cca gct ggt
                                                                       214
Leu Lys Arg Pro Trp Leu Leu Met Val Ala Pro Arg Leu Pro Ala Gly
        -15
                             -10
get agg gac tea gga cag ttt eec aga aaa gge caa geg gge age eec
                                                                       262
Ala Arg Asp Ser Gly Gln Phe Pro Arg Lys Gly Gln Ala Gly Ser Pro
                                         10
tcc agg ggc cgg gtg agg aag ctg ggg ggt gcg gtg gg
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Ser Arg Gly Arg Val Arg Lys Leu Gly Gly Ala Val
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<221> sig peptide
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tttatacaca cacacacaca cacactcata ttcattacat gtgtgtactt tctggttgct
                                                                       60
tcagtaggac ttttctaggc ttctttggac tatgtgtgat attttacttc agggactgaa
                                                                       120
tttcacaact gcctactatg caactttgtg attttcttga aagcacaakt actatatat
                                                                       180
a atg aaa atg tcc acc ccc tcc ccg ctt tct aaa aaa gtg ctc aga aac
                                                                      229
  Met Lys Met Ser Thr Pro Ser Pro Leu Ser Lys Lys Val Leu Arg Asn
      -30
cag gtc tca aga ttg rtt gcg ttg ctt tcc cca tac gct ttc act ctq
                                                                      277
Gln Val Ser Arg Leu Xaa Ala Leu Leu Ser Pro Tyr Ala Phe Thr Leu
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sct cgt ctt gcc tca ggg
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Xaa Arg Leu Ala Ser Gly
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gca aag gcc atc gca gaa gaa atg tgt rag caa gct gtg gta cat gga Ala Lys Ala Ile Ala Glu Glu Met Cys Xaa Gln Ala Val Val His Gly 1 5 10	159
ttt tct gca gat ctt cac tgt att agt gaa tcc gat aag gtc tcg gtg Phe Ser Ala Asp Leu His Cys Ile Ser Glu Ser Asp Lys Val Ser Val 20 25 30 att cag aat aca cct act ttt gca acg ggg ggg cgg g	207
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gtg ctt aga gaa aat ctg ttt gta aac ctg aat ctc tgt ttt gcc tac Wal Leu Arg Glu Asn Leu Phe Val Asn Leu Asn Leu Cys Phe Ala Tyr -15 -10 -5	162
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ttt																	101
Phe	Pro	Leu	Ser	Cys	Ser	Pro	Ser	Leu	Pro	Leu	Ser	Ile 1	Pro	Asp	Cys		
ctg	cct	gcc	ttc	ctc	tgg	ccġ	ctg	999	ata	ccc	tgg	cct	gat	gga	gag		149
Leu	Pro	Ala	Phe	Leu		Pro	Leu	Gly	Ile		Trp	Pro	Asp	Gly			
5			aat	<b>t</b> a a	10	a++	ata			15	~~~				20		107
ggt															CCT Pro		197
				25	5				30	5				35			
ctc																	245
Leu	Ser	Leu	Phe 40	Ala	Met	Leu	Ser	Gly 45	Arg	Glu	Gly	Ala	Pro 50	Leu	Leu		
atc	ccc	ctg						33	•				50			<b>'</b> •	255
Val		_	_														
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cttt	ttcg	itc t	gggc	tgcc	a ac	_	_	_	_	_			_		tct:		52
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tcc	tta	cca	aca	gag	acc	cct	aag	саа	-10	,				- 5			82
Ser																	
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ttc	ctgg	acc	gcgc	tgga	ag c	cctg	gcgg	c gg	cggc	cc a M	tg g et G	ly x	sc t aa L 105	tg g eu A	cg ct la Le	g u	56
сус Хаа	gcc Ala -10	Trp	ctg Leu	cag Gln	ccc Pro	agg Arg -95	tat Tyr	agg Arg	aag Lys	aat Asn	gcg Ala -90	tat Tyr	ctt	ttc Phe	atc Ile	. 1	.04
Tyr -85	Tyr	Leu	Ile	Gln	Phe -80	Cys	Gly	Хаа	Ser	tgg Trp -75	ata Ile	ttt Phe	Ala	Asn	Met -70	1	52
Thr	Val	Arg	Phe	Phe -65	Ser	Phe	Gly	Lys	Asp	tca Ser	Met	Val	Asp	Thr	ttt Phe	2	00
Tyr	Ala	Ile	Gly -50	Leu	Val	Met	Arg	Leu -45	Cys	caa Gln	Ser	Val	Ser	Leu	Leu	2	48
Glu	Leu	Leu -35	His	Ile	Tyr	Val	Gly	Ile	Glu	tca Ser	Asn	His -25	Leu	Leu	Pro		96
Arg	Phe -20	Leu	Gln'	Leu	Thr	Glu -15	Arg	Ile	Ile	Ile	Leu	Phe	Val	Val		' 3	44
Thr -5	Ser	Arg	Arg	Gly	Ser 1	Pro	Thr	Arg	Asn 5	atg Met	Trp	Суѕ	Val	Cys 10	Tyr	3	92
Ser	Ser	Leu	Asp 15	Leu	Trp	Ile	Trp	Leu 20	Xaa	aca Thr	Leu	ata Ile	gca Ala 25	tgk Xaa	tda Xaa	4	40
tca Ser	gtc Val	ata Ile 30	gga Gly	ata Ile	tcc Ser	tat Tyr	gct Ala 35	gtc Val	t tg Leu	aca Thr	t ·					4	74
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<b>~</b> <i>L L J</i> .	SC	ore 4	4.400 TLTAI	0000	0953				- `					•			
gatci	actc	at go tt ct	tgaga	atato	ato	ctto	cttc	agg	gaga	taa 🤈	ggaa	aaaa	ag c	caca	accca gggtc g atg Met	12 17	50 20 79
gac a Asp 1	Thr I	ttc o Phe I -15	ect tero s	ct d Ser I	ett a Leu T	hr I	etg a Leu : -10	act o	gcc Ala	tta ( Leu )	Leu	gtg ( Val :	cct a	agt . Ser .	aga	. 22	27
gtt d Val (	_			ig												24	1
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                                                                        120
 ggttgctagg gctgggggaa ctcagattgc ttcacctgtg gtatcagaca tcacaac
                                                                        177
 atg ggg ctc acc aag cag tac cta cgc tat gtt gct agt gcg gtc ttt
                                                                        225
 Met Gly Leu Thr Lys Gln Tyr Leu Arg Tyr Val Ala Ser Ala Val Phe
 -20
                     -15
                                          -10
 ggc gtt atc ggc agc caa aaa ggt aat att gtc ttt gtg aca ctt cgt
                                                                       273
 Gly Val Ile Gly Ser Gln Lys Gly Asn Ile Val Phe Val Thr Leu Arg
ggt gag aaa gga cgt tat gtg gca gta cca gct tgt gaa cac gtt ttc
                                                                       321
Gly Glu Lys Gly Arg Tyr Val Ala Val Pro Ala Cys Glu His Val Phe
         15
                             20
atc wgg gac tta agg aaa gga gag aag att ctt atc ctt cag ggg ctt
                                                                       369
Ile Xaa Asp Leu Arg Lys Gly Glu Lys Ile Leu Ile Leu Gln Gly Leu
                         35
ada caa gaa gtt act tgc tta tgc ccc tcc cca gat ggg cta cac tta
                                                                       417
Lys Gln Glu Val Thr Cys Leu Cys Pro Ser Pro Asp Gly Leu His Leu
                     50
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gct gtt ggg tat g
                                                                       430
Ala Val Gly Tyr
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                                                                      120
gcagaagcct cgctgaatcc cagccagctg gttctaacct tccagaatcg caatcccttc
                                                                      180
tececacage cagecetege egageaagea geaggatgtt tgeagtgteg egeceaggge
                                                                      240
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271 totgagactg agootgocat coactogoac gootttottt cagggotttt oggotgttgg ctacactgat gtgacccccc tecetttttg ga atg atg ggg atc ttt ttg gtg Met Met Gly Ile Phe Leu Val tat gtn gga ttt gtt ttc ttt tcc gtt tta tat gta caa caa ggg ctt, 401 Tyr Val Gly Phe Val Phe Phe Ser Val Leu Tyr Val Gln Gln Gly Leu -15 -10 tct tct caa gca 413 Ser Ser Gln Ala 1 <210> 503 <211> 167 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 26..166 <221> sig\_peptide <222> 26..91 <223> Von Heijne matrix score 4.40000009536743 seg WVLDPALLLTCLT/FP gaatcggaca acttaaagtc tcgat atg agc ctc gga ttg cat tcg aac tcc 52 Met Ser Leu Gly Leu His Ser Asn Ser -20 tgg gtt cta gac cca gct ctg cta cta act tgt ctg acc ttc.ccc att 100 Trp Val Leu Asp Pro Ala Leu Leu Leu Thr Cys Leu Thr Phe Pro Ile -10 -5 tat aaa ctg ttg tgg gtg aga ggt ggg acw agg wga act ctr wgr gcv 148 Tyr Lys Leu Leu Trp Val Arg Gly Gly Thr Arg Xaa Thr Leu Xaa Ala 10 ctg cac tcg gcg cgg acg g 167 Leu His Ser Ala Arg Thr 20 25 <210> 504 <211> 420 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 217..420 <221> sig peptide <222> 217..396 <223> Von Heijne matrix score 4.40000009536743 seq MWVXCXFCFVLFC/FE <221> misc feature <222> 47..48,368..369,373 <223> n=a, g, c or t

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272	
gattgtaagg agaggcggtc ccggtgtcct cgggtcccag gtgattgtga agtgctgacc aattgccact ggacatactt gaaacaaaat aggaaa atg gca gca aac tct tca  Met Ala Ala Asn Ser Ser	180 234
-60 -55 gga caa ggt ttt caa aac aaa aat aga gtt gca atc ttg gca gaa gtg	282
Gly Gln Gly Phe Gln Asn Lys Asn Arg Val Ala Ile Leu Ala Glu Leu -50 -45 -40 aca aag aga aaa gaa aac tac tta tgc aga acc agt ctt caa caa atc	
Thr Lys Arg Lys Glu Asn Tyr Leu Cys Arg Thr Ser Leu Gln Gln Ile -35 -30 -25	330
atc ctg gar cta ggt att gac act ata atg tgg gtt tnn tgt ntg ttt  Ile Leu Glu Leu Gly Ile Asp Thr Ile Met Trp Val Xaa Cys Xaa Phe -20 -15 -10	378
tgt ttt gtt ttg ttt tgt ttt gag acg gag tct cgc cct gtc Cys Phe Val Leu Phe Cys Phe Glu Thr Glu Ser Arg Pro Val -5	420
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agc gcg aca cat cct gga gct ggc ggc cgc agc aaa tgg gac caa Ser Ala Thr His Pro Gly Ala Gly Gly Arg Arg Ser Lys Trp Asp Gln -30 -25 -20	102
cca gct cca gcc cca ctt ctc ttc ctc ccg cca gcg gcc cca ggt ggg Pro Ala Pro Ala Pro Leu Leu Phe Leu Pro Pro Ala Ala Pro Gly Gly -15 -10 -5 1	150
gag gtc acc agc agt ggg gga agt cct ggg gsc acc aca gct gct cct Glu Val Thr Ser Ser Gly Gly Ser Pro Gly Xaa Thr Thr Ala Ala Pro 5 10 15	198
tca gga gcc ttg gat gct gct gct gtg gct gcc aag att aat gcc Ser Gly Ala Leu Asp Ala Ala Ala Ala Val Ala Ala Lys Ile Asn Ala 20 25 30	246
atg ctc atg gca aaa ggg aag ctg aaa cca act cag rat gct tct gag Met Leu Met Ala Lys Gly Lys Leu Lys Pro Thr Gln Xaa Ala Ser Glu	294
aag ctt cag gct cct ggc aaa ggc cta act agc aat aaa agc aag gat Lys Leu Gln Ala Pro Gly Lys Gly Leu Thr Ser Asn Lys Ser Lys Asp	342
gac ctg gtg gta gct gaa gta gaa att aat gat gtg cct ctc aca tgt Asp Leu Val Val Ala Glu Val Glu Ile Asn Asp Val Pro Leu Thr Cys	390
70 75 80 agg aac ttg ctg act cga gga cag ann caa gac gag atc agc cga ctt	438

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Arg Asn Leu Leu Thr Arg Gly Gln Xaa Gln Asp Glu Ile Ser Arg Leu
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                                  90
 agt ggg gct gca gta tca a
                                                                        457
 Ser Gly Ala Ala Val Ser
         100
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                                                                         60
 ttettetetg tggeeeteee etttgtetet teetttetgt ttteteetgt agtteeteet
                                                                        120
 cttctctccc ctgattgctc atg agt ccc ctt gat cag gct gta ata cgt gct
                                                                        173
                       Met Ser Pro Leu Asp Gln Ala Val Ile Arg Ala
                            -20
                                                -15
 gig tgt ctc agt gga ggt tcc tgc tgg gga gga gtc cgt tgt ctt gtg
                                                                        221
 Val Cys Leu Ser Gly Gly Ser Cys Trp Gly Gly Val Arg Cys Leu Val
 -10
                     -5
 cgt ggg ggc ccg aac ata ggc cct gca gcc cag ctg ctt ggg ggc att
                                                                        269
 Arg Gly Gly Pro Asn Ile Gly Pro Ala Ala Gln Leu Leu Gly Gly Ile
             10
                                 15
 cca etc tgc tgg cca eca get gtg act gca ggt gaa gtg aaa etg e
                                                                       315
 Pro Leu Cys Trp Pro Pro Ala Val Thr Ala Gly Glu Val Lys Leu
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cgtcgagcct gcgcactctg cctgagaccc tcgacccagc ccggctcctg tcctcctgta
                                                                       120
ttcctgcagt ccttttaagg aagaaaagtg a atg aac tca ttt cat ttt att
                                                                       172
                                    Met Asn Ser Phe His Phe Ile
                                    -15
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<220>

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                                                                        208
 Xaa Phe Leu Pro Phe Pro Trp Ala Glu Xaa Ala Gln
              -5
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                                                                         60
 aggg atg ggc tgg cac tca cat agt tcc caa ggc gtg caw gca atg cct
                                                                        109
      Met Gly Trp His Ser His Ser Ser Gln Gly Val Xaa Ala Met Pro
                      -25
                                          -20
 ctg ctg ctg tcc aca cac acc tgg aca gac aca gcc ctg gca ttc agc
                                                                       157
 Leu Leu Ser Thr His Thr Trp Thr Asp Thr Ala Leu Ala Phe Ser
                 -10
                                      -5
 aca cac aca cac
                                                                       169
 Thr His Thr His
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      seq WFLRSWTWPQTAG/RV
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                                                                        50
             Met Xaa Ala Val Arg Asn Ala Gly Ser Trp Phe Leu Arg
                      -20
                                          -15
tcc tgg act tgg ccc cag aca gcc ggc agg gtc gtg gcc aga rsg ccq
                                                                        98
Ser Trp Thr Trp Pro Gln Thr Ala Gly Arg Val Val Ala Arg Xaa Pro
                 -5
gcc ggg acc atc tgc aca gg
                                                                       118
Ala Gly Thr Ile Cys Thr
        10
<210> 510
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                                                                       120
gtgccatcat tccgattccg attttaacag caacctgctg atttcctgcc atagtttcct
                                                                       180
actiticcatt ctgagecect ttaatccact tatacaatat aactacteec tgaattattt
                                                                       240
ggtcatacca cttgtatctg ccgaacccct attcctcccc tggggtacgt tttccactaa
                                                                       300
acacacag ggaaatgcca cccaaatagc tct atg tgt gcc ttg ttc att ctt
                                      Met Cys Ala Leu Phe Ile Leu
                                      -15
gtt tcc att tct ttg ttt tat gca ctt ttt atc tct cca tcc ata caa
                                                                       402
Val Ser Ile Ser Leu Phe Tyr Ala Leu Phe Ile Ser Pro Ser Ile Gln
<210> 511
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                                                                      120
tagcattgat agaggaagcc cagcctggtg tgcacagc atg tac ctg gtg tgc aca
                                                                      176
                                          Met Tyr Leu Val Cys Thr
                                                       -50
aca tgc acc tgg tgt gta ttt tct gaa atg ttt gtt cat gga tta aac
                                                                      224
Thr Cys Thr Trp Cys Val Phe Ser Glu Met Phe Val His Gly Leu Asn
                            -40
                                                -35
atc act cag ctc gtg ctg agc cag ctg gat tac ttt ttc cat tcc aat
                                                                      272
Ile Thr Gln Leu Val Leu Ser Gln Leu Asp Tyr Phe Phe His Ser Asn
                                            -20
ctg aca aac ttg gtc ttg tat ttc tta gtc cat tta ctt ttt tcc ctt
                                                                      320
Leu Thr Asn Leu Val Leu Tyr Phe Leu Val His Leu Leu Phe Ser Leu
                    -10
age ctg ttt atg ccg ctg acg gg
                                                                      343
Ser Leu Phe Met Pro Leu Thr
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WO 99/53051
                                                                PCT/IB99/00712
                                       276
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                                                                        48
       Met Lys Leu Lys Leu Tyr Leu Cys Ile Leu Gly Pro Trp Gly
                    -75
                                        -70
tgc aak rkc aaa gta cca cta att ggg ttt ctt aaa aga ata aan hta
                                                                        96
Cys Xaa Xaa Lys Val Pro Leu Ile Gly Phe Leu Lys Arg Ile Xaa Xaa
                -60
tat nwt ctc aca gtt ctg aaa cct agd agt ctg ara tca ann tca gca '
                                                                       144
Tyr Xaa Leu Thr Val Leu Lys Pro Xaa Ser Leu Xaa Ser Xaa Ser Ala
            -45
                                 -40
ggg ttg gtt cct tct gag gac tct aaa aaa gaa tct gtt tca tgc ctc
                                                                       192
Gly Leu Val Pro Ser Glu Asp Ser Lys Lys Glu Ser Val Ser Cys Leu
                             -25
tet eet agg tte tgg tgg etg gga age etg akt gtt act tgg ett
                                                                       240
Ser Pro Arg Phe Trp Trp Leu Gly Ser Leu Xaa Val Thr Trp Leu
                         -10
ata cat gca tca ctc cag tct ctg tct cct ttt tct cat gcc att ttc
                                                                      288
Ile His Ala Ser Leu Gln Ser Leu Ser Pro Phe Ser His Ala Ile Phe
tca tgt gtc tct gtg ttt tcc ttt gct tat aag gat acc agt cat att
                                                                      336
Ser Cys Val Ser Val Phe Ser Phe Ala Tyr Lys Asp Thr Ser His Ile
           20
                                25
gaa tta ggg cct gct cta ata acc tca tct caa tta cct ctg caa gga
                                                                      384
Glu Leu Gly Pro Ala Leu Ile Thr Ser Ser Gln Leu Pro Leu Gln Gly
                            40
acc aat ttc caa ata atg tca cac tca cat gta gca
                                                                      420
Thr Asn Phe Gln Ile Met Ser His Ser His Val Ala
    50
                        55
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	20	
cta ctg gga acg gaa cag aaa caa aaa aa	-30 og atg gga aat ctg aag	. 28
Leu Leu Gly Thr Glu Gln Lys Gln Lys Lys Ar	g Met Gly Asn Leu Lys	,
-25 -20 ctg cta ttt ctt att ctg atc tta ata gca gg	-15	32
Leu Leu Phe Leu Ile Leu Ile Leu Ile Ala Gl	y Tyr Arg	32
-10 -5	1	
210 514		
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seq SALMLPLGCAVRT/RM		
-400- F14		
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ctccccatc gcaacccaca ggagggtttc cctcactct	g cctcctccaw cqcaccccca	6 12
kggaggtgtt ttccctcact ggttctgttg gtggcggtg	g cagcaatccg agtcacatqq	18
caccagagta tgtcacgggt ggcggatctg a atg ggg		23
met Gly	Leu Gln Ser Leu Thr	
ett eca gtg tet tge age eet tet gee etg at	g ctt ccc ttg gga tgt	28
Leu Pro Val Ser Cys Ser Pro Ser Ala Leu Me	_ <del>_</del>	
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Ala Val Arg Thr Arg Met Leu	•	30
1	•	
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stocctagat ttcaagcatg tataatcact caaagtggat	atgatcacag gcattettet	120 180
ttgagetca geaaaactat geetaceaac acegaagaga	agtcaaagat ttttatgaaa	240
aaaattgca gatgatgttg gtgagataat aggatatgag	g caatgaaccc ttgggtgggg	300
tccagggca cttaaattgc ctcgtgtctt gagtccttaa		356
	Met Asp Ser Asn Lys -30	
aa tta gta tta tca ata aca ggt aat act gtg		404
ws Len Val Leu Ser Tle Thr Gly Acn Thr Val		

278 -20 tta gaa tca tta gct ggc agt gtc aam tct gaa caa gat ttg tca gct 452 Leu Glu Ser Leu Ala Gly Ser Val Xaa Ser Glu Gln Asp Leu Ser Ala -5 tat 455 Tyr <210> 516 <211> 360 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 196..360 <221> sig\_peptide <222> 196..336 <223> Von Heijne matrix score 4.40000009536743 seq SFXXCLFLXLXXS/EM <221> misc\_feature <222> 330..332 <223> n=a, g, c or t <400> 516 aagagegttg ggeagatata gtetgtagat atttttgaaa egtetttggg tttgteecat 60 ttggggtttg ctcagcttct tgaatctgta ggttttgggg atcccccamc ctgcaaattt 120 ggtgatattt ttgctcttat ttctkcaagt gaacttgaaa tcccaccctg ttggtttct 180 cettetaaga etetg atg acg tgt atg tta gee tgt agg tgt agt ete amg 231 Met Thr Cys Met Leu Ala Cys Arg Cys Ser Leu Xaa -45 -40 ggt ecc caa gat tit egt tie tge tet gte tit tet etg tig etc aag 279 Gly Pro Gln Asp Phe Arg Phe Cys Ser Val Phe Ser Leu Leu Leu Lys -35 -30 -25 -20 ttg ggt aat ttc tat ttt tct ttt wct dtc tgt ctw ttt ctw dta ctd 327 Leu Gly Asn Phe Tyr Phe Ser Phe Xaa Xaa Cys Leu Phe Leu Xaa Leu -15 -10 wyn nnt tot gag atg gag tom cac tot tto ago 360 Xaa Xaa Ser Glu Met Glu Ser His Ser Phe Ser 5 . <210> 517 <211> 453 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 113..451 <221> sig\_peptide <222> 113..307 <223> Von Heijne matrix score 4.40000009536743 seq FIEAALLIHGSAC/VY <400> 517 attttcctgg gcgggaacag caaaatggcg ccagaactag tggcgggctg aggacgccgt 6.0 accectegga aggeageeet geggteeett tgeegeeegt teeeteeegg ac atg gag 118

Met Glu

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gac gtg gag gcg cgc ttc gcc cac ctc ttg cag ccc atc cgc gac ctc
                                                                        166
 Asp Val Glu Ala Arg Phe Ala His Leu Leu Gln Pro Ile Arg Asp Leu
              -60
                                  -55
 acc aag aac tgg gag gtg gac gtg gcg gcc cag ctg ggc gag tat ctg
                                                                        214
 Thr Lys Asn Trp Glu Val Asp Val Ala Ala Gln Leu Gly Glu Tyr Leu
                             -40
                                                  -35
 gag gag ctg gat cag atc tgc att tct ttt gac gaa ggc aag acc aca
                                                                        262
 Glu Glu Leu Asp Gln Ile Cys Ile Ser Phe Asp Glu Gly Lys Thr Thr
                         -25
                                              -20
 atg aac ttc att gag gca gcg ttg ttg atc cat ggc tct gcc tgc gtc
                                                                        310
 Met Asn Phe Ile Glu Ala Ala Leu Leu Ile His Gly Ser Ala Cys Val
                     -10
                                          -5
 tac agt aag aag gtg gaa tac ctc tac tca ctc gtc tac cag gcc ctt
                                                                        358
 Tyr Ser Lys Lys Val Glu Tyr Leu Tyr Ser Leu Val Tyr Gln Ala Leu
                                 10
 gat ttc atc tct gga aag agg cgg gcc aag cag ctc tct tcg gtg cag
                                                                        406
 Asp Phe Ile Ser Gly Lys Arg Arg Ala Lys Gln Leu Ser Ser Val Gln
                             25
 gag gac agg gcc aat ggg gtt gca gct ccg ggg tcc cca gga ggc ag
                                                                        453
 Glu Asp Arg Ala Asn Gly Val Ala Ala Pro Gly Ser Pro Gly Gly
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                                                                        60
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ggagacgcaa g atg gcg gct gtg gtg ctg gcg gcg acg cgg ttg ctg cgg  Met Ala Ala Val Val Leu Ala Ala Thr Arg Leu Leu Arg  -10  -5  ggc tcg ggt tct tgg ggc tgt tcg cgg ctg agg ttt gga cct cct gcg Gly Ser Gly Ser Trp Gly Cys Ser Arg Leu Arg Phe Gly Pro Pro Ala  1  5  10  15  tac aga cgg ttt agt agt ggt ggt gcc tat ccc aac atc ccc ctc tct Tyr Arg Arg Phe Ser Ser Gly Gly Ala Tyr Pro Asn Ile Pro Leu Ser  20  25  30  tct ccc tta cct gga gta ccc aag cct gtt ttt gct aca gtt gat gga Ser Pro Leu Pro Gly Val Pro Lys Pro Val Phe Ala Thr Val Asp Gly  35  40  45  cag gaa aag ttt gaa acc aaa gta acc aca ttg gat aat ggg ctt cgc Gln Glu Lys Phe Glu Thr Lys Val Thr Thr Leu Asp Asn Gly Leu Arg  50  55  60	98 146
ggagacgcaa g atg gcg gct gtg gtg ctg gcg gcg acg cgg ttg ctg cgg  Met Ala Ala Val Val Leu Ala Ala Thr Arg Leu Leu Arg  -10  -5  ggc tcg ggt tct tgg ggc tgt tcg cgg ctg agg ttt gga cct cct gcg Gly Ser Gly Ser Trp Gly Cys Ser Arg Leu Arg Phe Gly Pro Pro Ala  1  5  10  15  tac aga cgg ttt agt agt ggt ggt gcc tat ccc aac atc ccc ctc tct Tyr Arg Arg Phe Ser Ser Gly Gly Ala Tyr Pro Asn Ile Pro Leu Ser  20  25  30  tct ccc tta cct gga gta ccc aag cct gtt ttt gct aca gtt gat gga Ser Pro Leu Pro Gly Val Pro Lys Pro Val Phe Ala Thr Val Asp Gly  35  40  45  cag gaa aag ttt gaa acc aaa gta acc aca ttg gat aat ggg ctt cgc Gln Glu Lys Phe Glu Thr Lys Val Thr Thr Leu Asp Asn Gly Leu Arg  50  gtg gca tct cag aat aag ttt gga cag ttt tgt aca gta gga att ctt Val Ala Ser Gln Asn Lys Phe Gly Gln Phe Cys Thr Val Gly Ile Leu  65  70  75	98 146 194
ggagacgcaa g atg gcg gct gtg gtg ctg gcg gcg acg cgg ttg ctg cgg  Met Ala Ala Val Val Leu Ala Ala Thr Arg Leu Leu Arg  -10  -5  ggc tcg ggt tct tgg ggc tgt tcg cgg ctg agg ttt gga cct cct gcg Gly Ser Gly Ser Trp Gly Cys Ser Arg Leu Arg Phe Gly Pro Pro Ala  1  5  10  15  tac aga cgg ttt agt agt ggt ggt gcc tat ccc aac atc ccc ctc tct Tyr Arg Arg Phe Ser Ser Gly Gly Ala Tyr Pro Asn Ile Pro Leu Ser  20  25  30  tct ccc tta cct gga gta ccc aag cct gtt ttt gct aca gtt gat gga Ser Pro Leu Pro Gly Val Pro Lys Pro Val Phe Ala Thr Val Asp Gly  35  40  45  cag gaa aag ttt gaa acc aaa gta acc aca ttg gat aat ggg ctt cgc Gln Glu Lys Phe Glu Thr Lys Val Thr Thr Leu Asp Asn Gly Leu Arg  50  gtg gca tct cag aat aag ttt gga cag ttt tgt aca gta gga att ctt Val Ala Ser Gln Asn Lys Phe Gly Gln Phe Cys Thr Val Gly Ile Leu  65  70  75	98 146 194 242
ggagacgcaa g atg gcg gct gtg gtg ctg gcg gcg acg cgg ttg ctg cgg  Met Ala Ala Val Val Leu Ala Ala Thr Arg Leu Leu Arg  -10  -5  ggc tcg ggt tct tgg ggc tgt tcg cgg ctg agg ttt gga cct cct gcg Gly Ser Gly Ser Trp Gly Cys Ser Arg Leu Arg Phe Gly Pro Pro Ala  1 5 10 15  tac aga cgg ttt agt agt ggt ggt gcc tat ccc aac atc ccc ctc tct Tyr Arg Arg Phe Ser Ser Gly Gly Ala Tyr Pro Asn Ile Pro Leu Ser  20 25 30  tct ccc tta cct gga gta ccc aag cct gtt ttt gct aca gtt gat gga Ser Pro Leu Pro Gly Val Pro Lys Pro Val Phe Ala Thr Val Asp Gly  35 40 45  cag gaa aag ttt gaa acc aaa gta acc aca ttg gat aat ggg ctt cgc Gln Glu Lys Phe Glu Thr Lys Val Thr Thr Leu Asp Asn Gly Leu Arg  50  gtg gca tct cag aat aag ttt gga cag ttt tgt aca gta gga att ctt Val Ala Ser Gln Asn Lys Phe Gly Gln Phe Cys Thr Val Gly Ile Leu  65 70  atc aat tca gga tcg aga tat ga Ile Asn Ser Gly Ser Arg Tyr	98 146 194 242 290

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gtctaggctc ttcaagttag gattcatatc tatgacatgt gctgtacagt gcttctactg
                                                                        60
tgaggtagtc tcccagacag aaaccacatg ggccttcagg catagatggt cagtaaataa
                                                                       120
ttactttaca gtggtgtcat ttcttaggag acmcagagtr agaccttaag tgagatctta
                                                                       180
cctacctcct cccatccaat ctatccatac aaggttggac ctaaagcagc cttgagctta
                                                                       240
ataatgatgt gtgttagaac aaggatactg agattagact aagntggttc tttaagtcag
                                                                       300
ccgtctctga caaagggcac aca atg tac tgt ctg arg tgt gtg gag aaa ata
                                                                       353
                           Met Tyr Cys Leu Xaa Cys Val Glu Lys Ile
                           -25
                                               -20
gca aaa gct ctt tat ctc agc ctt aat tta tat ttt gca aat tca ctt
                                                                       401
Ala Lys Ala Leu Tyr Leu Ser Leu Asn Leu Tyr Phe Ala Asn Ser Leu
-15
                     -10
                                         -5
tat tat atg tgt gtg tgt tca tac ata tac ttt tat tta tkt att tat
                                                                       449
Tyr Tyr Met Cys Val Cys Ser Tyr Ile Tyr Phe Tyr Leu Xaa Ile Tyr
                                 10
                                                     15
ktk tat kkt tta ata aaa ann dng tot tat tat gtt gcc cag act ggt
                                                                       497
Xaa Tyr Xaa Leu Ile Lys Xaa Xaa Ser Tyr Tyr Val Ala Gln Thr Gly
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ctc aa
                                                                       502
Leu
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                                                                       49
           Met Cys Gln Leu Arg Arg Gly Leu Gly Lys Arg Pro Leu
                           -25
agt gag gcg tcg gct gtg ttt ctc acc gcg gtc ttt tcc tcc cac tct
                                                                       97
Ser Glu Ala Ser Ala Val Phe Leu Thr Ala Val Phe Ser Ser His Ser
tgg ctg gtt ggå ccc cgc tat
                                                                      118
Trp Leu Val Gly Pro Arg Tyr
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tttacgtttg ctgaggagag ctttacttcc aactatgtgg tcgattttgg aataggtgtg
                                                                       120
gtgcggtgct gaaaaaaatg tatattctgt tgatttgggg tggagagttc tgtag atg
                                                                       178
tot gtt agg too act tgg tgc aga got cag tto aat too tgg gta too
                                                                       226
Ser Val Arg Ser Thr Trp Cys Arg Ala Gln Phe Asn Ser Trp Val Ser
                     -25
                                        -20
ttg tta act ttc tgc ctc att gat ctg tct aat gtt gac agt ggg amg'
                                                                       274
Leu Leu Thr Phe Cys Leu Ile Asp Leu Ser Asn Val Asp Ser Gly Xaa
                                     - 5
gg
                                                                       276
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cttcgcctcc ttcaccgccg cagacccctt caagttctag tc atg gtg agt ggg
                                                                       114
                                               Met Val Ser Gly
                                                             -50
gtt ccc tcg ggg ctg ggg aag agt gcg cgt ccc agg gga cgg cgg gcc
                                                                       162
Val Pro Ser Gly Leu Gly Lys Ser Ala Arg Pro Arg Gly Arg Arg Ala
                -45
                                    -40
cgg aaa cta Ctg cct gca cct cgg gcc gcg ccc agg aca gct cca gac
                                                                       210
Arg Lys Leu Leu Pro Ala Pro Arg Ala Ala Pro Arg Thr Ala Pro Asp
            -30
                                -25
tac ecc ggg ecc etc egg tta acc tgg ett gtg geg gee ggg etg gaa
                                                                       258
Tyr Pro Gly Pro Leu Arg Leu Thr Trp Leu Val Ala Ala Gly Leu Glu
                            -10
ggt cga gtt cac ttg gca gac acc agt tcg ggc cgg aaa acc tgg ccc
                                                                       306
Gly Arg Val His Leu Ala Asp Thr Ser Ser Gly Arg Lys Thr Trp Pro
                                        10
ggg tgc ggc cat cag tgg aaa tgg aaa gcc ctc ttg atc cta gtg agg
                                                                       354
Gly Cys Gly His Gln Trp Lys Trp Lys Ala Leu Leu Ile Leu Val Arq
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                                                         30
gct ttc ccc gca
                                                                       366
Ala Phe Pro Ala
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                                                                       60
tgttttgtct aaaattcata gatgctgaac tgtgtatatt tgttgtcaag tttgaaaggt
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acttgggttt ttgggggtgt taggaggtag ggtggatgtt actattaaat acatttagaç
                                                                      180
tttttaaaat aagtgtaact gatcatttcc aacaaatatt tactatgtcc atacttgtgc
                                                                      240
tccaaaagac aattetgtet teetettgag atacatgtet eggggeeeet gtaggtetgg
                                                                      300
tetgagaggg teece atg ggt gge tgt gte wge tgg ege ttt ett gga cae
                 Met Gly Gly Cys Val Xaa Trp Arg Phe Leu Gly His
                     -30
                                          -25
tee tet get etc agg act gtg tgt age agt etg ege tea gya agg eea
                                                                      399
Ser Ser Ala Leu Arg Thr Val Cys Ser Ser Leu Arg Ser Xaa Arg Pro
                -15
                                    -10
tgt tgg tgt gat ggg ctt cgg ctc aga tg
                                                                      428
Cys Trp Cys Asp Gly Leu Arg Leu Arg
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                                                                       60
acaaaccgga cccgcaacca cc atg aac agc aaa ggt caa tat cca aca cag
                                                                      112
                         Met Asn Ser Lys Gly Gln Tyr Pro Thr Gln
                             -50
cca acc tac cct gtg cag cct cct ggg aat tcc agt ata ccc tca qac
                                                                      160
Pro Thr Tyr Pro Val Gln Pro Pro Gly Asn Ser Ser Ile Pro Ser Asp
                        -35
ctt gca tct tcc tca ggc tcc acc cta tac cga tgc tcc acc tqc cta
                                                                      208
Leu Ala Ser Ser Ser Gly Ser Thr Leu Tyr Arg Cys Ser Thr Cys Leu
                    -20.
                                        -15
ctc aga gct cta tcg tcc gag ctt tgt gca ccc agg ggc tgc cac agt
                                                                      256
Leu Arg Ala Leu Ser Ser Glu Leu Cys Ala Pro Arg Gly Cys His Ser
               -5
                                    1
ccc cac cat gtc agc cgc att tcc tgg acc ctc tct gta tct tcc cat
                                                                      304
Pro His His Val Ser Arg Ile Ser Trp Thr Leu Ser Val Ser Ser His
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	10					15					20				•	
ggc cca Gly Pro	gtc Val	tgt Cys	ggc Gly	tgt Cys	tgg Trp 30	gcc Ala	ttt Phe	agg Arg	ttc Phe	cac His 35	aat Asn	ccc Pro	cat His	ggc Gly		352
tta tta Leu Leu 40	tcc Ser	agt Ser	cgg Arg	tcc Ser 45	cat His	cta Leu	tcc	amc Xaa	tgg Trp 50	ctc	cac His	agt Ser	gct Ala	ggt Gly 55	ı ·	400
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	81	33 eijne 4.30	e ma1	0190	7348	6					. •			٠	· ·	
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ggg tct Gly Ser	Pro	Ser -5	Val	Ala	Gln	Ser	Gly 1	Val	Gln	Trp	Cys 5	Asp	Leu	Gly		157
tta ctg Leu Leu 10	Gln	Pro	Pro	Pro	Pro 15	Gly	Phe	Lys	Arg	Phe 20	Ser	tgc Cys	ctc Leu	agc Ser		205
ctc cta Leu Leu 25	Gly	Xaa	Xaa	Asp 30	Cys	aga Arg	Arg	Ala	Pro 35	Pro	ggg Gly					244
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gtc atg	ttt	gtg	tct	gka	aca	rcg	ttt	ttc	ttt	kcg	ctc	ckc	ttt	ctg	,	168
	Phe			-20					-15					-10	•	
ggc atg Gly Met	ttc   Phe	Leu :	tct Ser -5	ggc Gly	atg Met	gtg Val	gct Ala	caa Gln 1	att Ile	gat Asp	gct Ala	aac Asn 5	tgg Trp	aac		216
ttc ctg	gat 1	ttt 9	gcc	tac	cat	ttt	aca	gta	ttt	gtc	ttc	tat	ttt	gga		264

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Phe Leu Asp Phe Ala Tyr His Phe Thr Val Phe Val Phe Tyr Phe Gly
                             15
gcc ttt tta ttg gaa gca gcc aca tcc ctg cat gat ttg cat tgc
Ala Phe Leu Leu Glu Ala Ala Ala Thr Ser Leu His Asp Leu His Cys
                         30
aat aca acc ata acc rgg cag cca ctc ctg agt gat aac cag tat aac
                                                                       360
Asn Thr Thr Ile Thr Xaa Gln Pro Leu Leu Ser Asp Asn Gln Tyr Asn
                     45
                                         50
ata aac gta gca gcc tca att ttt gcc ttt atg acg aca gct tgt tat
                                                                       408
Ile Asn Val Ala Ala Ser Ile Phe Ala Phe Met Thr Thr Ala Cys Tyr
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ggt tgc agt ttg ggt ctg gct tta cg
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Gly Cys Ser Leu Gly Leu Ala Leu
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<222> 384
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                                                                       60
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                                                                      120
tgttgactaa atgaatttag gtctggacct tgatggctta atgtctttct aaaaatctac
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ttccatatet aageetttet tgaetaettt egeettttte tgtgaaetta aaagtettta
                                                                      240
ttcattgttt gccggatgct aaacatttac aaaagtaatc ctt atg tca tct gaa
                                                                      295
                                                Met Ser Ser Glu
                                                     -25
att ttc taw ktt dtk cak att gck tat gct tda tat ttg cta gtt ggt
                                                                      343
Ile Phe Xaa Xaa Xaa Ile Ala Tyr Ala Xaa Tyr Leu Leu Val Gly
                            -15
ctt ttc cct cta aaa tgc cac wag agt hat ttt tct aag tna caa atc
                                                                      391
Leu Phe Pro Leu Lys Cys His Xaa Ser Xaa Phe Ser Lys Xaa Gln Ile
tca tca ttt gtg gaa
                                                                      406
Ser Ser Phe Val Glu
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<222> 23..76

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                                                                         52
                          Met Ala Ala Ser Ser Leu Thr Val Thr Leu
                                       -15
 ggg cgg ctg gcg tcc gcg tgc agc cac agc atc ctg aga cct tcg ggg
                                                                       100
 Gly Arg Leu Ala Ser Ala Cys Ser His Ser Ile Leu Arg Pro Ser Gly
 ecc gga gca gcc tec ett tgg tet get tet ega agg tte aat tea cag
                                                                       148
Pro Gly Ala Ala Ser Leu Trp Ser Ala Ser Arg Arg Phe Asn Ser Gln
     10
                         15
age act tea tat eta cea gga tat gtt evt aaa aca tee etg agt tea
                                                                       196
Ser Thr Ser Tyr Leu Pro Gly Tyr Val Xaa Lys Thr Ser Leu Ser Ser
                     30
                                         35
cca cct tgg ccg agg g
                                                                       212
Pro Pro Trp Pro Arq
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totggaatto cagaa atg tta att got got tgt att tgt tot tgt ttg ttt
                                                                       111
              Met Leu Ile Ala Ala Cys Ile Cys Ser Cys Leu Phe
                             -15
ttt agc cag tat ttg gsy ytt tct aat cca gcc gcg gg
                                                                       149
Phe Ser Gln Tyr Leu Xaa Xaa Ser Asn Pro Ala Ala
    -5
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aag Lvs	tgc Cvs	tgg	g gtt v Val	cto Lev	ago Sen	c tac	ato	g tgg	g cag	g agt	gca	tct	cto	g ggt	Met ttt Phe	106
-15					-10	0			•	- 5		•		1 613	nne 1	
Ser	Asn	Arg	g act g Ile 5	Lys	Sei	r Xaa	Lev	g aga 1 Arg 10	e cct	cca Pro	gca Ala	ggc Gly	: ,			145
	_		_					10				٠.	•			
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aaat	cct	cag	caga	tttt	tg t	tcaa	gagc	t gc	ttcc	agat	tgg	cttc	tag	ctqc	cagtgt	60
gacc	ttg	ggc (	agaa	cctt	ca a	tg t	ct g	tg g	gg c	tg t	gt t	tt c	tt a	tc t le T	gg caa rp Gln	113
atg Met	gga Gly	att Ile	atg Met -55	cts Leu	ttg Leu	cct Pro	cgg Arg	gaa Glu -50	tgt Cys	tgg Trp	aag Lys	gtc Val	aaa Lys -45	gac Asp	agt	161
aag Lys	aag Lys	tac Tyr -40	aaa Lys	agc Ser	tgc Cys	aga Arg	gaa Glu -35	tca Ser	gta Val	ctg Leu	cct Pro	gca Ala -30	caa	qca	tgt Cys	209
aca Thr	gga Gly -25	gag Glu	tcc Ser	cct Pro	gtc Val	tta Leu -20	tct	gga Gly	gtc Val	agg Arg	gtt Val -15	cta	999 Gly	atc Ile	cgc Arg	257
ctc Leu : -10	tcg Ser	tgc Cys	gtg Val	tta Leu	tcc Ser -5	cat	ctc Leu	caa Gln	gcc Ala	tgg Trp 1	gac	tcc Ser	tgg Trp	Asp	aat Asn	305
cag a	aag Lys	gtg Val	tgc Cys 10	tac Tyr	ctg	ggt Gly	gca Ala	ccc Pro 15	tgc Cys	ttt	999 Gly	aaa Lys	agg Arg 20	5 ctg Leu	agt Ser	353
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<223	· Vo	n He	ijne													
				0000 CSGS												
	ت د	7	10		/	~										

<223> n=a, g, c or t

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aaacaaatac actaaaa atg ttc gct ttc ctg gcc ggg tgc agt ggc tca
                                                                       110
                   Met Phe Ala Phe Leu Ala Gly Cys Ser Gly Ser
                                    -10
tgc ctg tgg tcc cgg cac ttc ggg aga ctg cgg cgg gct ccc ttg
                                                                       158
Cys Leu Trp Ser Arg His Phe Gly Arg Leu Arg Arg Ala Ala Pro Leu
                                                 10
ago coa gag ttt gag aco ggo ctg ggt aac atg gtg gaa ccc caa tgg g
                                                                       207
Ser Pro Glu Phe Glu Thr Gly Leu Gly Asn Met Val Glu Pro Gln Trp
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cctttgtgcc tctggctgct ccaacatcac agatgccatc ctgaatgctc taggtcagaa
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                              Met Pro Thr Tyr Phe Leu Phe Val Pro
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cat ttg att tca tgt aat tgg tgt gaa cca agg ggt aac aat ccc caa
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His Leu Ile Ser Cys Asn Trp Cys Glu Pro Arg Gly Asn Asn Pro Gln
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Thr
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ctt tgg acc agt ttc cag aat cct ctt cag gta gtg ctt ctc acc agc	287
Leu Trp Thr Ser Phe Gln Asn Pro Leu Gln Val Val Leu Leu Thr Ser	
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Val Ser Leu Xaa Xaa Xaa Xaa Xaa Gly Ser Val Arg Ile Xaa Leu	335
-10 -5 1 5	
tet eac tgg tea age tea gee tte tte tte etd att ewb nek kyw hwt	383
Ser His Trp Ser Ser Ser Ala Phe Phe Phe Leu Ile Xaa Xaa Xaa Xaa	
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-10 -5 1	
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5 10 15	
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-2	u Pn O	e se	r Lei	u 11	e Ar	g Se: 5	r Hi	s Le	u Se	r Il: -1:	e Lei O	u Ala	a Pho	e Vai	gcc l Ala -5		281
Il	t gc e Al	t tt a Ph	t gg: e Gl:	t gti y Vai 1	t tte	g ga u As <sub>l</sub>	e at	g aa t Ly: 5	g tc s Se	r Le	pro	c acg	g cca r Pro 10	a ggg	9 9		327
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gaa Glu -55 acg Thr act	aat Asn cgg Arg ggg	gtc Val agg Arg aac	tat Tyr ctc Leu agc Ser	ggt Gly atc Ile -35 atc	tta Leu -50 ctt Leu ctg	gc a Mo- gaa Glu gtt Val ggc Gly	tg get G 55 gag Glu ggg Gly cag Gln	ga g ly G aac Asn aga Arg aga Arg	ga a ly A gct Ala aca Thr -30 cgg Arg	gg a rg L cag Gln -45 ggg Gly ttc Phe	ag a ys M tcc Ser gcc Ala ttc	tg g et A 60 cgg Arg ggg Gly tcc Ser	cg a la T cag Gln aag Lys agg Arg	gag Glu agc Ser -25 ctg Leu	tcc Ser -40 gcc Ala 999 Gly	a	161
gaa Glu -55 acg Thr act Thr	aat Asn cgg Arg ggg Gly acg	gtc Val agg Arg aac Asn tct Ser	tat Tyr ctc Leu agc Ser -20 gtg Val	ggt Gly atc Ile -35 atc Ile anc	tta Leu -50 ctt Leu ctg Leu agg	gc a Monday Market Mark	tg get G 55 gag Glu ggg Gly cag Gln tgc Cys 1	ga g ly G aac Asn aga Arg aga Arg -15 acc Thr	ga ally A gct Ala aca Thr -30 cgg Arg acg Thr	gg a rg L cag Gln -45 ggg Gly ttc Phe grh Xaa	ag a ys M tcc Ser gcc Ala ttc Phe agc Ser 5	tg g et A 60 cgg Arg ggg gly tcc Ser cgc Arg	cg a la T cag Gln aag Lys agg Arg -10 agg Arg	gag Glu agc Ser -25 ctg Leu tgg	at gasp Gl tcc Ser -40 gcc Ala ggg Gly gac Asp	a	<ul><li>113</li><li>161</li><li>209</li></ul>
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gaa Glu -55 acg Thr act Thr gcc Ala aag Lys 10 tgt Cys	aat Asn cgg Arg ggg Gly acg Thr tgc Cys cca Pro > 54	gtc Val agg Arg aac Asn tct Ser -5 cac His aga Arg	tat Tyr ctc Leu agc Ser -20 gtg Val gtg Val cag Gln	ggt Gly atc Ile -35 atc Ile anc Xaa Glu atc Ile 30	tta Leu -50 ctt Leu ctg Leu agg Arg gtc Val 15 ctg	gc a Mc a	tg gget G 55 gag Glu ggg Gly cag Gln tgc Cys l gnd Xaa	ga g ly G aac Asn aga Arg aga -15 acc Thr ctm Leu	ga aly Algorithms gga acg Thr gga acg Arg acg Arg arg arg Arg	gg a rg L cag Gln -45 gGly ttc Phe grh Xaa cat His 20 gag	ag a ys M tcc Ser gcc Ala ttc Phe agc Ser vwk Xaa	tg get A 60 cgg Arg ggg Gly tcc Ser cgc Arg can Xaa	cg a la T cag Gln aag Lys agg Arg -10 agg Arg	gag Glu agc Ser -25 ctg Leu tgg Trp	at gasp Gl tcc Ser -40 gcc Ala 999 Gly gac Asp aag Lys	a	113 161 209 257 305
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                                                                       120
gaagccacag aacaaaacat acgagctggt acccaggcag ttttgcaggt ggatcacttt
                                                                       180
atggctattt ttaaaaataa aataatcatt aaatatttct gttcagtatt tcagtataca
                                                                       240
gtatactttt cacaatataa aaatagaagc ttaatactgg gcattcatac tttttaaaga
                                                                       300
gnatga atg aag aaa tog gtt too tgo tgt agt tot ota tgg gta agt
                                                                       348
       Met Lys Lys Ser Val Ser Cys Cys Ser Ser Leu Trp Val Ser
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                                -10
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                                                                      120
gtgrgacttg gggccctttc gtgcctgatg ggaagctcct gcmaccccgg ggagccctc
                                                                      180
cagactgtcc ttgcccacct ggctgcactg gcctctttat gccaacccag tgaggacagg
                                                                      240
ttctgaggga cctggacag atg ctg ctc cta gcc atg gct gga cga tgt
                                                                      292
                     Met Leu Leu Pro Leu Ala Met Ala Gly Arg Cys
                     -30
                                         -25
                                                              -20
tat aca gcc aag cac agc acw gtg ctg ctc tca gga agc cca agg gct
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Tyr Thr Ala Lys His Ser Thr Val Leu Leu Ser Gly Ser Pro Arg Ala
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Lys Tyr Pro Leu His Ala Ile Arg Arg Tyr Leu Ser Thr Leu Arg Ass	1
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Gln Arg Ala Glu Glu Gln Val Ala Arg Phe Gln Lys Ile Pro Asn Gly	,
25 30 35	, e
gaa aat gag aca atg att cct gta ttg aca tca aaa aaa gca agt gaa	239
Glu Asn Glu Thr Met Ile Pro Val Leu Thr Ser Lys Lys Ala Ser Glu	
40 45 50 55 tta cca gtc agt gaa gtt gca agc att ctc caa gct gat ctt cag aat	287
Leu Pro Val Ser Glu Val Ala Ser Ile Leu Gln Ala Asp Leu Gln Asr	201
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                                                                      112
                               Met His Ile Cys Leu Phe Phe Ser
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Phe Ser Xaa Xaa Phe Xaa Leu Phe Phe Phe Phe
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catcataaat aatgaccatg aaaatgtaaa atatcttcct ggacacaagc tgccagaaa
                                                                     239
atg tgg ttg cca tgt caa atc tta gcg agg ctg tgc agg atg cag acc
                                                                     287
Met Trp Leu Pro Cys Gln Ile Leu Ala Arg Leu Cys Arg Met Gln Thr
                -15
                                    -10
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Cys Trp Cys Leu Ser Phe Pro Thr Ser Ser Phe Thr Glu Ser Val Met
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cacagt															17
	25		_		_									o Ser	
*										-8	-				
gag aa															22
Glu Ly	s Gly	Thr	Lys		Pro	Ser	Val	Glu	_	Gly	Phe	Gln	Thr		, .
-75	a sta	ac+		-70 ++a	~~~	~++	22+	C2.C	-65		a+ a			-60	
cct ct Pro Le															26
PIO DE	u IIC	****	-55	Deu	GIU	vai	A511	-50	,DCu	GIII	Бец	PIO	-45	PIO	
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Glu Ly															
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aac aa															36
Asn Ly	s Gly -25	гàг	Pne	Arg	val		Lys	He	Ala	Glu		Thr	Val	Thr	
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Ile Le															71.
-1					- 5				,	1				5	
gtg gt	t tac	aaa	gcc	ttc	acc	tat	gat	cac	agc	tgc	сса	gag	gat	tcg	46
Val Va	1 Tyr	Lys		Phe	Thr	Tyr	Asp		Ser	Cys	Pro	Glu	Asp	Ser	
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ctc ct															160
Leu Le	u rne	vag	-5	TIG	ıyr	ırp	GIÀ	GIN	TAL	wig	ınr	ASP 5	GIÀ	TTG	
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Gly As															200
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tct ttt ctt tct ttc ttt t Ser Phe Leu Ser Phe Phe I -10			
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agt aaa ctt tta tta ttt t Ser Lys Leu Leu Leu Phe S		t tta ara aaa g	cr cgc atg 214
awt aca gca gca cct ggg Xaa Thr Ala Ala Pro Gly 10	•	J	232
<210> 554 <211> 141			

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                                                                         54
                                   Met Val Thr Pro Val His Ile Leu-
 aca gcc gtg ctt cca ctt gtg tct cac cag caa aac cat ctg ggt gga
                                                                        102
 Thr Ala Val Leu Pro Leu Val Ser His Gln Gln Asn His Leu Gly Gly
 agg ttt gca tct ctg gga tcc tca ggc att agg cac ggg
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 Arg Phe Ala Ser Leu Gly Ser Ser Gly Ile Arg His Gly
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 atctttccat tttttgaggt ctanncaatc tcttttatca gtgtktccta attctgatta
 tagagatett teacatettt gntteaagtt gatteetaeg tattteaett tatttgtgge
                                                                       240
 tgttgtaaat gggattactt tttgcatttc tttchnnsaa ttgttcagtc agcatacagg
                                                                       300
 aatgatactg attittgt atg ttg att tta cat ctt gca act tta cta aat
                                                                       351
                     Met Leu Ile Leu His Leu Ala Thr Leu Leu Asn
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                                         -10
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 Leu Phe Ile Ser Ser Asn Ser Phe
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tteeteteee teltaceeee accetgtaca aaatgeataa aggatggaaa aactactgea
                                                                       120
gccagaagtc tttgaatgag gcatcaatgg atgaatattt aggcagctta gggctgtttc
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gaaagetgae tgecaagg atg eet ett gee tet tte ggg eea ttt egg age
                    Met Pro Leu Ala Ser Phe Gly Pro Phe Arg Ser
                     ~15
agt tgt ttt gca gcc agg tcc atc att tgg aaa tca gga agg caa ggg
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Ser Cys Phe Ala Ala Arg Ser Ile Ile Trp Lys Ser Gly Arg Gln Gly
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ctgtgtacta taaagtattt ttattggtat ttagtcttgc tgttattgtt gctaatgatt
                                                                       120
gtattgaata attaccagct gttgttagtt atttgaaatt aggtgcctaa agcaacctct
                                                                       180
catcttgcag aaagtcatct ttcttgaaac tttttaaaaa cttgcttgaa ac atg gag
                                                                       238
                                                           Met Glu
act tgg aat ggg acg tot atc ata gta gca cat ctg ara tcc ttc tca
                                                                       286
Thr Trp Asn Gly Thr Ser Ile Ile Val Ala His Leu Xaa Ser Phe Ser
                -25
                                     -20
tte etg etg tea ttt etg tee ttt ege agt eea ett tgt eae eae eee
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Phe Leu Leu Ser Phe Leu Ser Phe Arg Ser Pro Leu Cys His His Pro
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ctc ggg
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Leu Gly
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Leu	Ser -10	Leu	Ile	Phe	Ala	Ser	Cys			acc Thr						344
			tgt Cys											•	-	365
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aata ccct aag Lys	ttai ggta agc Ser	atg agg Arg	gga Gly	ccc Pro -45	ckt Xaa	gtc Val	cag Gln	act Thr	ctg Leu -40	ggg Gly	ag a l cat His	det v gct Ala	gtc a Val 1 ggc Gly	acc thr s aac aac Asn -35	tca Ser -50 ctg Leu	
aata ccct aag Lys agg Arg	agc Ser agt Ser	agg Arg ctg	gga Gly cgg Arg	ccc Pro -45 gag Glu	ckt Xaa tgg Trp	gtc Val cct Pro	cag Gln gat Asp	act Thr ctg Leu	ctg Leu -40 tgc Cys	ggg Gly tgc Cys	cat His ttg	gct Ala agg Arg	gtc a Val  ggc Gly ctt Leu -20	acc f Thr s aac Asn -35 ttt Phe	ser -50 ctg Leu gtc Val	114
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aata ccct aag Lys agg Arg cca Pro gtc Val	agc ser agt ser gat Asp ttc Phe	agg Arg ctg Leu cac His -15 cct	gga Gly cgg Arg -30 act Thr	ccc Pro -45 gag Glu gta Val cag	ckt Xaa tgg Trp ctt Leu gtc Val	gtc Val cct Pro gct Ala acc	cag Gln gat Asp ctg Leu -10 tgc Cys	act Thr ctg Leu -25 gtg Val aga Arg	ctg Leu -40 tgc Cys tgc Cys	ggg Gly tgc Cys cac His cca Pro 10	ag a Cat His ttg Leu agc Ser agg Arg	gct Ala agg Arg gca Ala -5 aca	gtc a Val 1 ggc Gly ctt Leu -20 tcc Ser ggg Gly	acc in the state of the state o	Ser -50 ctg Leu gtc Val tct Ser cat His	114 162 210
aata ccct aag Lys agg Arg cca Pro gtc Val	agc agc agc agc agc true agc	agg Arg ctg Leu cac His cct Pro	gga Gly cgg Arg -30 act Thr tct ser	ccc Pro -45 gag Glu gta Val cag Gln	ckt Xaa tgg Trp ctt Leu gtc Val 5	gtc Val cct Pro gct Ala acc Thr	cag Gln gat Asp ctg Leu -10 tgc Cys	act Thr ctg Leu -25 gtg Val aga Arg	ctg Leu -40 tgc Cys tgc Cys	ggg Gly tgc Cys cac His cca	cat His ttg Leu agc Ser agg Arg	gct Ala agg Arg gca Ala -5 aca Thr	gtc a Val 1 ggc Gly ctt Leu -20 tcc ser ggg Gly cac	acc from Service Associated Assoc	Ser -50 ctg Leu gtc Val tct Ser cat His 15 aat	114 162 210 258
aata ccct aag Lys agg Arg cca Pro gtc Val	agc agc agc agt agc agt tc agt tc agt tc agt tc agt tc agc agc agc agc agc agc agc agc agc ag	agg Arg ctg Leu cac His cct Pro tgc Cys	gga Gly cgg Arg -30 act Thr tct ser	ccc Pro -45 gag Glu gta Val cag Gln atc	ckt Xaa tgg Trp ctt Leu gtc Val 5	gtc Val cct Pro gct Ala acc Thr	cag Gln gat Asp ctg Leu -10 tgc Cys	act Thr ctg Leu -25 gtg Val aga Arg	ctg Leu -40 tgc Cys tgc Cys ctc Leu ttt	ggg Gly tgc Cys cac His cca Pro 10 cac	cat His ttg Leu agc Ser agg Arg	gct Ala agg Arg gca Ala -5 aca Thr	gtc a Val 1 ggc Gly ctt Leu -20 tcc ser ggg Gly cac	aac Asn -35 ttt Phe atc Ile tca Ser cca Pro	Ser -50 ctg Leu gtc Val tct Ser cat His 15 aat	114 162 210 258 306
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                                                                       120
cttggtgmga gaaatcccag atcctgtgat gggggacacc agtgagg atg cct cga
                                                                       176
                                                     Met Pro Arg
tcc atc gat ksg aag gca ctg atc tgg act gtc agg ttg gtg gtc tta
                                                                       224
Ser lle Asp Xaa Lys Ala Leu Ile Trp Thr Val Arg Leu Val Val Leu
                 -20
                                     -15
                                                         -10
ttt gcn agt cca awa gtg cgg cca gcg agc agc atg tct tca agg ctc
                                                                       272
Phe Ala Ser Pro Xaa Val Arg Pro Ala Ser Ser Met Ser Ser Arg Leu
            -5
ctg ctc ccc gsc ctt cat tac tcg gac tgg act tgc tgg ctt cct gaa
                                                                       320
Leu Leu Pro Xaa Leu His Tyr Ser Asp Trp Thr Cys Trp Leu Pro Glu
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cgg aga ga
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Arg Arg
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                                                                      110
         Met Thr Ser Leu Leu Thr Thr Pro Ser Pro Arg Glu Glu Leu
                         -50
                                              -45
atg acc acc cca att tta cag ccc act gag gcc ctg tcc cca gaa gat
                                                                      158
Met Thr Thr Pro Ile Leu Gln Pro Thr Glu Ala Leu Ser Pro Glu Asp
                    -35
                                        -30
gga gcc agc aca gca ctc att gca gtt gtt atc acc gtt gtc ttc ctc
                                                                      206
Gly Ala Ser Thr Ala Leu Ile Ala Val Val Ile Thr Val Val Phe Leu
                -20
                                    -15
acc ctg ctc tcg gtc gtg atc ttg atc ttc ttt tac ctg tac aag aac
Thr Leu Leu Ser Val Val Ile Leu Ile Phe Phe Tyr Leu Tyr Lys Asn
            - 5
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WO 99/53051 PCT/IB99/00712 302 aaa ggc agc tac gtm nnn tat gaa cct aca gaa ggt gag ccc agt gcc 302 Lys Gly Ser Tyr Val Xaa Tyr Glu Pro Thr Glu Gly Glu Pro Ser Ala atc gtc cag atg gag adw nnc ttg gcc aag ggc agc gag 341 Ile Val Gln Met Glu Xaa Xaa Leu Ala Lys Gly Ser Glu 30 <210> 562 <211> 484 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 334..483 <221> sig\_peptide <222> 334.:387 <223> Von Heijne matrix score 4.19999980926514 seq LIYLVSSFLALNQ/AS <400> 562 gttagttggg cagggctgaa gtgtatgtgg tgaggaaaag aggctcctac tgtagacagc 60 cttgttctac agatcctccc agaaatctct gggccaggtg gaacccaggg tcagagaggg 120 atgggagaga ggtttaattt tccatgataa ataaaaatct ataaaataat aaacaagaga 180 aaagagattg gaaacagcca ggttggagca gtgagtgagt aaggaaacct ggctgccctc 240 tccagattcc ccaggctctc agagaagatc agcagaaagt ctgcaagass ctaagaacca 300 tcagccctca gctgcacctc ctcccctcca agg atg aca aag gcg sgv ctc atc 354 Met Thr Lys Ala Xaa Leu Ile tat ttg gtc agc agc ttt ctt gcc cta aat cag gcc agc ctc atc agt 402 Tyr Leu Val Ser Ser Phe Leu Ala Leu Asn Gln Ala Ser Leu Ile Ser -10 -5 cgc tgt gac ttg gcc cag gtg ctg cag ctg gag gac ttg gat ggg ttt 450 Arg Cys Asp Leu Ala Gln Val Leu Gln Leu Glu Asp Leu Asp Gly Phe gag ggt tac tcc ctg agt gac tgg ctg tgc tgg c 484 Glu Gly Tyr Ser Leu Ser Asp Trp Leu Cys Trp <210> 563 <211> 229 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 122..229 <221> sig\_peptide <222> 122..190 <223> Von Heijne matrix score 4.19999980926514 seq QLILLGIFRGIRH/QI <400> 563 gaaaggcete gaaggcageg teetactega ceaceaagge aagacaagee acetekattt 60

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a atg gca cag tta ata atg tgg ctc aag aac cag tta ata ctc ttg ggg Met Ala Gln Leu Ile Met Trp Leu Lys Asn Gln Leu Ile Leu Leu Gly

ata ttt cgg gga ata aga cac cag att tat cta atc aga act ctt cag

-15

-20

120

217

303

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atc agg caa tgg
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Ile Arg Gln Trp
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                                                                       112
                      Met Gly Pro Val Pro Gly Ala Ala Ala Gly Val
                      -30
                                          -25
rgg ccc ayg amt ggc gaa ctt gcg grg acc ctg tcc ctc acc tgc agt
                                                                       160
Xaa Pro Xaa Xaa Gly Glu Leu Ala Xaa Thr Leu Ser Leu Thr Cys Ser
                 -15
                                     -10
gtc tct ggt gtc tcc atc act agt tat tac tgg agc tgg atc cgc car
                                                                       208
Val Ser Gly Val Ser Ile Thr Ser Tyr Tyr Trp Ser Trp Ile Arg Gln
gcc cca ggg aag ggg ccg gag tgg atc ggg cdk atc gat cat agc ggg
                                                                       256
Ala Pro Gly Lys Gly Pro Glu Trp Ile Gly Xaa Ile Asp His Ser Gly
                       20
                                             25
gat acc gac tac aat ccc tcc ctc cag agt cga gtc acc ctc tca gtg
                                                                       304
Asp Thr Asp Tyr Asn Pro Ser Leu Gln Ser Arg Val Thr Leu Ser Val
                    35
                                         40
gac acg tcg aag aac cag ttc tca ctg agg ttg ctt tct gtg agc gca
                                                                       352
Asp Thr Ser Lys Asn Gln Phe Ser Leu Arg Leu Leu Ser Val Ser Ala
                50
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ccagttggag gcatctgtcc accc atg tgg ttc cag aca cgt tca tgt ggc
                                                                      111
                           Met Trp Phe Gln Thr Arg Ser Cys Gly
                               -35
cac cat gac ccc gtc ggc atc aca ggg gta acc aag gtg atc ctc cct
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seq LSLPSFLCTCCQF/FP

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His His Asp Pro Val Gly Ile Thr Gly Val Thr Lys Val Ile Leu Pro
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                                                  -15
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                                                                       113
                              Met Ser Tyr Val Val Thr Lys Thr Lys
                                               -105
 gcg att aat ggg aaa tac cat cgt ttc ttg ggt cgt cat ttc ccc cgc
                                                                       161
 Ala Ile Asn Gly Lys Tyr His Arg Phe Leu Gly Arg His Phe Pro Arg
 -100
                     -95
                                         -90
 ttc tat gtc ctg tac aca atc ttc atg aaa gga ttg cag atg tta tgg
                                                                       209
 Phe Tyr Val Leu Tyr Thr Ile Phe Met Lys Gly Leu Gln Met Leu Trp
                 -80
                                      -75
 gct gat gcc aaa aag gct aga aga ata aag aca aat atg tgg aag cac
                                                                       257
 Ala Asp Ala Lys Lys Ala Arg Arg Ile Lys Thr Asn Met Trp Lys His
           -65
                                 -60
 aat ata aag ttt cat caa ctt cca tac cgg gag atg gag cat ttg aga
                                                                       305
 Asn Ile Lys Phe His Gln Leu Pro Tyr Arg Glu Met Glu His Leu Arg
                             -45
 cag ttc cgc caa gac gtc acc aag tgt ctt ttc cta ggt att att tcc
                                                                       353
 Gln Phe Arg Gln Asp Val Thr Lys Cys Leu Phe Leu Gly Ile Ile Ser
                         -30
                                             -25
att cca cct ttt gcc aac tac ctg gtc ttc ttg cta atg tac ctg ttt
                                                                       401
Ile Pro Pro Phe Ala Asn Tyr Leu Val Phe Leu Leu Met Tyr Leu Phe
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ccc agg caa cta ctg atc agg
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ttc cca cat gat cc Phe Pro His Asp Pr 1 5	a att agc ( O Ile Ser (	tct cag tac agt Ser Gln Tyr Ser 10	tct cca caa ggg aaa Ser Pro Gln Gly Lys 15	152
cca tgt caa gta ac Pro Cys Gln Val Th 20	c tac aag t r Tyr Lys 1	ttc ttg ttt att Phe Leu Phe Ile 25	ttg ctt gga cac gtc Leu Leu Gly His Val	200
tat ccc aga gat gg Tyr Pro Arg Asp Gl 35				218
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ggg gct ggg gct gtg Gly Ala Gly Ala Val -60	gct gcg c Ala Ala P	cg ccg gcc atc ro Pro Ala Ile -55	gac ttt ccc gcc gag Asp Phe Pro Ala Glu -50	97
ggc ccg gac ccc gaa	Tyr Asp G	aa tct gat gtt	cca gca kaa atc cag Pro Ala Xaa Ile Gln -35	145
gtg tta aaa gaa ccc Val Leu Lys Glu Pro ~30	cta caa c Leu Gln G -25	ln Pro Thr Phe	cct ttt gca gtt gca Pro Phe Ala Val <b>A</b> la -20	193
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<222> 133..243

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seq SISFLPFQASIFG/KT

acd profit fire in

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219

288

-35 -30 -25 aaa acc ttc ctt gcc ccc atg acc aac tgc cac tca att tcc ttt ctt Lys Thr Phe Leu Ala Pro Met Thr Asn Cys His Ser Ile Ser Phe Leu

-20 -15 -10

cct ttc caa gca agt att ttt gga aag act cgt ctg cag tca ctg agg 267

Dro Dho Clo Ala Ser Ila Bha Cly Lys Thr Arg Lov Clo Ser Lov Arg

Pro Phe Gln Ala Ser Ile Phe Gly Lys Thr Arg Leu Gln Ser Leu Arg
-5 1 5
cct tcc cac cct tac ccc cac

Pro Ser His Pro Tyr Pro His 10 15

<210> 577

<211> 264

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                                                                        120
  aagttteeta gta atg eee aag gat get gae etg get tte agt get tea
                                                                        169
                 Met Pro Lys Asp Ala Asp Leu Ala Phe Ser Ala Ser
                                 -35
 ttg ttt gaa aga gca gag tcc ctt tat act ctg att tca aaa ttt ktt
                                                                        217
 Leu Phe Glu Arg Ala Glu Ser Leu Tyr Thr Leu Ile Ser Lys Phe Xaa
          -25
                              -20
 tet tgt dtk tgt gtg tet ace ttg gca tat act aaa gga agg ggg
                                                                        264
 Ser Cys Xaa Cys Val Ser Thr Leu Ala Tyr Thr Lys Gly Arg Gly
      -10
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 ttcttagttc cagttacttt attgtasytt tttnhttgty ytttactgtg tgtg atg
                                                                        117
 ttt gtg aat aga acc tgt ttt aat tct tcc ttt cca atc tgg atg cct
                                                                        165
 Phe Val Asn Arg Thr Cys Phe Asn Ser Ser Phe Pro Ile Trp Met Pro
                              -20
 ttt ctt ttt ctt aca tta ttc cac tgc tta gga cgt cgg g
                                                                        205
 Phe Leu Phe Leu Thr Leu Phe His Cys Leu Gly Arg Arg
     -10
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-35

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tta ttg ata caa gat ctc act atg tca ccc act gct gga atg cag tgg Leu Leu Ile Gln Asp Leu Thr Met Ser Pro Thr Ala Gly Met Gln Trp -5 1 5	97
cat aat cat ggc cca cca caa gcc ttg cct tgc cca ctg aga abc cc His Asn His Gly Pro Pro Gln Ala Leu Pro Cys Pro Leu Arg Xaa 10 15 20	144
<210> 584 <211> 282 <212> DNA <213> Homo sapiens	
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ccttgtttaa gccgtgatcg tgacctcacc atgtgtagac agtgag atg tca ttt	55 103
ccttgtttaa gccgtgatcg tgacctcacc atgtgtagac agtgag atg tca ttt Met Ser Phe -45 ctc aat gtg gac atc aca gat tgc ctg tat aac ccc agt gtg tgt ccc Leu Asn Val Asp Ile Thr Asp Cys Leu Tyr Asn Pro Ser Val Cys Pro	٠,
ccttgtttaa gccgtgatcg tgacctcacc atgtgtagac agtgag atg tca ttt  Met Ser Phe  -45  ctc aat gtg gac atc aca gat tgc ctg tat aac ccc agt gtg tgt ccc Leu Asn Val Asp Ile Thr Asp Cys Leu Tyr Asn Pro Ser Val Cys Pro  -40  -35  gtg gct cag agc agt ctg acc tgt gac ttc ata gat ggt atc tgc ttg Val Ala Gln Ser Ser Leu Thr Cys Asp Phe Ile Asp Gly Ile Cys Leu  -25  -20  -15  ggg tcg cct ttg gct gag tgt ctg ctt ggt gna gwa wkw ksc att ttk Gly Ser Pro Leu Ala Glu Cys Leu Leu Gly Xaa Xaa Xaa Xaa Ile Xaa -10  -5  1  Ser Phe  -45  Ccc  Agt gtg tgt ccc  agt gag agt gtc gac ttc ata agt ggt atc tgc ttg  agt gat ggt atc tgc ttg  agt gat gtg ttg  agt gat acc tgc ttg  Asp Gly Ile Cys Leu  -25  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -15  -20  -20  -15  -20  -20  -15  -20  -20  -20  -20  -20  -20  -20  -2	103
ccttgtttaa gccgtgatcg tgacctcacc atgtgtagac agtgag atg tca ttt  Met Ser Phe  -45  ctc aat gtg gac atc aca gat tgc ctg tat aac ccc agt gtg tgt ccc Leu Asn Val Asp Ile Thr Asp Cys Leu Tyr Asn Pro Ser Val Cys Pro  -40  -35  gtg gct cag agc agt ctg acc tgt gac ttc ata gat ggt atc tgc ttg Val Ala Gln Ser Ser Leu Thr Cys Asp Phe Ile Asp Gly Ile Cys Leu  -25  -20  -15  ggg tcg cct ttg gct gag tgt ctg ctt ggt gna gwa wkw ksc att ttk Gly Ser Pro Leu Ala Glu Cys Leu Leu Gly Xaa Xaa Xaa Xaa Ile Xaa  -10  -5  ggr atc aat rns cym tgc ttt ccg tgt ggt gtg aag tgc gca ggt gtg Gly Ile Asn Xaa Xaa Cys Phe Pro Cys Gly Val Lys Cys Ala Gly Val  10  15  20	103 151
ccttgtttaa gccgtgatcg tgacctcacc atgtgtagac agtgag atg tca ttt  Met Ser Phe  -45  ctc aat gtg gac atc aca gat tgc ctg tat aac ccc agt gtg tgt ccc Leu Asn Val Asp Ile Thr Asp Cys Leu Tyr Asn Pro Ser Val Cys Pro  -40  gtg gct cag agc agt ctg acc tgt gac ttc ata gat ggt atc tgc ttg Val Ala Gln Ser Ser Leu Thr Cys Asp Phe Ile Asp Gly Ile Cys Leu  -25  -20  -15  ggg tcg cct ttg gct gag tgt ctg ctt ggt gna gwa wkw ksc att ttk Gly Ser Pro Leu Ala Glu Cys Leu Leu Gly Xaa Xaa Xaa Xaa Ile Xaa  -10  -5  ggr atc aat rns cym tgc ttt ccg tgt ggt gtg aag tgc gca ggt gtg Gly Ile Asn Xaa Xaa Cys Phe Pro Cys Gly Val Lys Cys Ala Gly Val	103 151 199
ccttgtttaa gccgtgatcg tgacctcacc atgtgtagac agtgag atg tca ttt  Met Ser Phe  -45  ctc aat gtg gac atc aca gat tgc ctg tat aac ccc agt gtg tgt ccc Leu Asn Val Asp Ile Thr Asp Cys Leu Tyr Asn Pro Ser Val Cys Pro  -40  gtg gct cag agc agt ctg acc tgt gac ttc ata gat ggt atc tgc ttg Val Ala Gln Ser Ser Leu Thr Cys Asp Phe Ile Asp Gly Ile Cys Leu  -25  ggg tcg cct ttg gct gag tgt ctg ctt ggt gna gwa wkw ksc att ttk Gly Ser Pro Leu Ala Glu Cys Leu Leu Gly Xaa Xaa Xaa Xaa Ile Xaa  -10  -5  ggr atc aat rns cym tgc ttt ccg tgt ggt gtg aag tgc gca ggt gtg Gly Ile Asn Xaa Xaa Cys Phe Pro Cys Gly Val Lys Cys Ala Gly Val  10  15  20  gtc ttg ggg ctg agc acc ctg tgg tat gtt gta gc Val Leu Gly Leu Ser Thr Leu Trp Tyr Val Val	103 151 199 247

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                                                                        53
                           Met Ala Ala Ser Val Leu Asn Thr Val Leu
                                           -20 .
agg egg ett eet atg eta tet ete tte ega ggt tet eay vvg rbg tte
                                                                       101
Arg Arg Leu Pro Met Leu Ser Leu Phe Arg Gly Ser His Xaa Xaa Phe
                 -10
                                     -5
agg ttc ccc tcc aga ctc ttt gca cca aag ctc cct ctg agg aag att
                                                                       149
Arg Phe Pro Ser Arg Leu Phe Ala Pro Lys Leu Pro Leu Arg Lys Ile
ctt tgt cct cag ttc cca ttt ctc ctt ata agg atg agc cct gga aat
                                                                       197
Leu Cys Pro Gln Phe Pro Phe Leu Leu Ile Arg Met Ser Pro Gly Asn
                        25
atc tgg aat cag aag aat acc agg agc gat atg gtt ctc gcc ccg tct
                                                                       245
Ile Trp Asn Gln Lys Asn Thr Arg Ser Asp Met Val Leu Ala Pro Ser
                    40
                                         45
ggg ctg act acc gcc gca acc aca agg gtg gtg tac ccc cac agc gga
                                                                       293
Gly Leu Thr Thr Ala Ala Thr Thr Arg Val Val Tyr Pro His Ser Gly
                55
                                    60
ctc gga aga cat gta ttc gtc gga ata aag ttg ttg gga atc cct gcc
                                                                       341
Leu Gly Arg His Val Phe Val Gly Ile Lys Leu Leu Gly Ile Pro Ala
                                75
cca tct gtc gag atc aca agt tgc atg ttg act tta g
                                                                      378
Pro Ser Val Glu Ile Thr Ser Cys Met Leu Thr Leu
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<221> misc_feature
<222> 218,224
<223> n=a, g, c or t
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cagccagcca tgcctccagt tcaggtactt ggcattgcta agctcagaac aggacttgcc
                                                                      120
agtgtctaga tgaaaaagag gagagatctc aagagggata accaattggc tggcaaagta
acaa atg aaa agt aac ctg act cta ttg acc tgc tta ncc ctg nat ggg
                                                                      229
    Met Lys Ser Asn Leu Thr Leu Leu Thr Cys Leu Xaa Leu Xaa Gly
```

WO 99/53051 PCT/JB9	99/
316	,,,,
15	
and des dus tous see dus dus des des des des des des des des des de	
Gly Glu Gly Trp Lys Gly Ala Ala Val Cys Phe Glu Thr Val Glu Gln	27
ttt tgc agc ctt aga aaa tgg gat gta aga tag ata aga tag	
ttt tgc agc ctt aga aaa tgg cat gta aca tac cta rcc aaa gac agc ' Phe Cys Ser Leu Arg Lys Trp His Val Thr Tyr Leu Xaa Lys Asp Ser 15 20 25	32
gga ctc tgt caa caa cag gag aag ctc tat acg aaa ttc ttg gtc tgc	37:
Gly Leu Cys Gln Gln Gln Glu Lys Leu Tyr Thr Lys Phe Leu Val Cys	٠,,
30 35 40 45	
ata aag gga gca tca aat gaa gaa att aag aaa acc tac a	41:
Ile Lys Gly Ala Ser Asn Glu Glu Ile Lys Lys Thr Tyr 50 55	
<210> 589	
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seq LASPCVLVQGSGX/SL	
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gaatgttcca tttctacpep gcaccaagag petercente	60
caccactoga coggang ato oto one tot one tot one tot oto oto oto	.20 .70
Met Leu Ala Ser Pro Cys Val Leu Val Gln Gly	,
-10 -5	
tet ggs bee age ett gte agg ace eee tgg tgt eea gag e	10
Ser Gly Xaa Ser Leu Val Arg Thr Pro Trp Cys Pro Glu	
1 5 10	
-010. 500	
<210> 590 <211> 178	
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seq ILLLITIIYSYL/ES	

<400> 590

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317

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Glu Ile Leu Leu Leu Ile Thr Ile Ile Tyr Ser Tyr Leu Glu Ser
                 -10
                                      -5
ttg gtg aag ttt ttc att cct cag agg aga aaa tct gtg gct ggg gag
                                                                       150
Leu Val Lys Phe Phe Ile Pro Gln Arg Arg Lys Ser Val Ala Gly Glu
                             10
att gtt ctc att act gga gct ggg cat g
                                                                       178
Ile Val Leu Ile Thr Gly Ala Gly His
    20
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                                                                      120
tcggggctgc rraattgcaa ccttgcca atg gac ctg atc ggt ttt ggt tat
                                                                       172
                               Met Asp Leu Ile Gly Phe Gly Tyr
gca gcc ctc gtg aca ttt gga agc att ttt gga tat aag cdg aga ggt
                                                                       220
Ala Ala Leu Val Thr Phe Gly Ser Ile Phe Gly Tyr Lys Xaa Arg Gly
                        -25
ggt gtt ccg tct ttg att gct ggt ctt ttt gtd gga tgt ttg gcc ggc
                                                                      268
Gly Val Pro Ser Leu Ile Ala Gly Leu Phe Val Gly Cys Leu Ala Gly
                    -10
tat nsa gct tac cgt gtc tcc aat gac aaa cga gat gta a
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Tyr Xaa Ala Tyr Arg Val Ser Asn Asp Lys Arg Asp Val
            5
                              , 10
<210> 592
<211> 219
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<222> 16..72
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sgg Xaa	cgg Arg	cgg Arg -5	ttg Leu	gta Val	acc Thr	ggt Gly	cag Gln 1	acc	agc	ccg Pro	aga Arg 5	999 999	acc	tgg	tgc Cys	99
Leu 10	Tyr	cca Pro	Gly	Phe	Cys 15	Arg	Ser	Val	Ala	Cys 20	Ala	Met	Pro	Cys	Cys 25	. 147
agt Ser	cac His	agg Arg	agc Ser	tgt Cys 30	aga Arg	gag Glu	gac Asp	ccc Pro	ggt Gly 35	aca Thr	tct Ser	gaa Glu	agc Ser	cgg Arg 40	gaa Glu	195
_		cgt Arg			_											219
<210 <211 <212 <213	> 21 > DN	.5	apie	ens				,								
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<221 <222		s 52	15				•									
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ttt a Phe :	Thr	aaa 9 Lys ( -15	gaa a Glu :	ata (	ggt Gly 1	Leu	att Ile -10	gga Gly	ctt Leu	aca Thr	gtt Val	cca Pro -5	tgt Cys	ggc Gly	tgg Trp	164
Gly s	agc Ser :	ctc a Leu 1	ata a [le ]	Thr I	atg ( Met 1 5	gca q Ala (	gaa Glu	ggc Gly	agg Arg	gag Glu 10	gag Glu	caa Gln	gtc Val	acg Thr	tct Ser 15	212
999 Gly																215
<210; <211; <212; <213;	> 16 > DN	1	npien	ns	,	-				•						
<220:		-														
		160	)	•												
<222>	89	pep 130 . Hei	ı		-i v					-						
	sco	ore 4				IF										
	tagt						c at	g ca	t tt	a g	ga ti	tc a	tt c			: 60 112

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 Phe His Gly Leu Ile Ala Asn Phe Phe Phe Cys Leu Asn Ala Pro Ala
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                                                                       120
tecetgeaga tettggggee ggaggeagnt ecaaceettg gageaggaag aaacgeaaag
                                                                       180
ttgtcaagaa ccaagtcgag ctgcctcaga gccggcccgc agtagctgca gactccgccc
                                                                       240
gcgacgtgtg cgcgcttctc tgggccagag cgagcctgtt ttgtgctcgg gttaagagat
                                                                       300
tigtecbage tatace atg gge ege act egg gaa get gge tge gtg gee get
                                                                       352
                   Met Gly Arg Thr Arg Glu Ala Gly Cys Val Ala Ala
                   -20
                                       -15
ggt gtg gtt atc ggg gct ggt gct gct act gtg tat aca gac tg
                                                                       396
Gly Val Val Ile Gly Ala Gly Ala Ala Thr Val Tyr Thr Asp
<210> 596
<211> 407
<212> DNA
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<220>
<221> CDS
<222> 228..407
<221> sig peptide
<222> 228..341
<223> Von Heijne matrix
      seq FKPXSCLSLLSNX/DY
<400> 596
tgagttttat gmttgattta tatcttttgg ttacaagtcc tttgtcagat atatgatttg
                                                                       60
caaatatttt ctcactctgg gtaggttgtc tttttacttt cttgataatg tcctcttttg
                                                                      120
ttgcttgtgt tatctccttt tttgtttttt attctttta aagttatctc ttacaggaag
                                                                      180
gattcctttt ttcttaaaaa agtttttcaa ttctttttt ttttgag atg gag tct
                                                                      236
                                                    Met Glu Ser
cac tot gto gcc cag gct agg atg cgg ysg caw aat oto ago toa otg
                                                                      284
His Ser Val Ala Gln Ala Arg Met Arg Xaa Xaa Asn Leu Ser Ser Leu
                    -30
                                        -25
caa cot ctg ccg cct ggg ttc aag cca tts tcc tgc ctm agc ctc ctg
                                                                      332
```

300

```
Gln Pro Leu Pro Pro Gly Phe Lys Pro Xaa Ser Cys Leu Ser Leu Leu
                  -15
                                      -10
 agt aay tsa gat tac agg cat gca cca cca ttc ctg gct aat ttt kgw
                                                                       380
 Ser Asn Xaa Asp Tyr Arg His Ala Pro Pro Phe Leu Ala Asn Phe Xaa
 att ttt cat aga gat gga gtt tca cca
                                                                        407
 Ile Phe His Arg Asp Gly Val Ser Pro
     15
 <210> 597
 <211> 274
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> CDS
 <222> 90..272
 <221> sig_peptide
 <222> 90..254
<223> Von Heijne matrix
       score 4
       seq LHQGLCLPQRVHC/SL
<400> 597
getgacegrg egeacseege ecceggsgee atetteeega eegegageeg tecaggtete
                                                                        60
agtgctrtgc ccccccaga gcctagagg atg ttt cat ggg atc cca gcc acg
                                                                       113
                                 Met Phe His Gly Ile Pro Ala Thr
                                 ~55
ccg ggc ata gga gcc cct ggg aac aag ccg gag ctg tat gag gta cga
                                                                       161
Pro Gly Ile Gly Ala Pro Gly Asn Lys Pro Glu Leu Tyr Glu Val Arg
                             -40
                                                 -35
caa cat ggc aga gct gtt tgc ggt ggt gaa gac aat gca agc cct gga
                                                                       209
Gln His Gly Arg Ala Val Cys Gly Glu Asp Asn Ala Ser Pro Gly
                       - -25
                                             -20
gaa ggc cta cat caa gga ctg tgt ctc ccc cag cga gta cac tgc agc
                                                                       257
Glu Gly Leu His Gln Gly Leu Cys Leu Pro Gln Arg Val His Cys Ser
-15
                    -10
ctg ctc ccg gct cct gg
                                                                       274
Leu Leu Pro Ala Pro
<210> 598
<211> 417
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 343..417
<221> sig_peptide
<222> 343..408
<223> Von Heijne matrix
      score 4
      seq LFLSVLNFLFLLS/FS
<400> 598
gcatctagaa gtacaagttg atgattattg tccatttgat agagacactg gaagggtgtc
                                                                       60
agtgtaaaca ctggccatgt gaagattgag cctgttgatg gtttcttttg tatcatagga
                                                                      120
tgccacgtca ccaactaggg aattctgccc aatcagttga gccaaatagt gctgtcctat
                                                                      180
tgtaaaattg tttaatctgt gtgcttgtgt gtgtgcttgt cagaatttgt gaatcataga
                                                                      240
attgttttaa ctggaagaag acccccaaga tcatctgctt caaccccttc cttcctctc
```

tttccagaga ggttgcactt tacttgagct gtgactagga tt atg cca cat tct  Met Pro His Ser  -20	,354
ttt gta agt tgt aac cta ttt ttg tct gtr ttg aat ttc ctt ttt ttg Phe Val Ser Cys Asn Leu Phe Leu Ser Val Leu Asn Phe Leu Phe Leu -15 -10 -5	402
cta agc ttt agc aca Leu Ser Phe Ser Thr 1	417
<210> 599 <211> 329 <212> DNA	
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<220> <221> CDS	
<222> 240329	
<pre>&lt;221&gt; sig_peptide &lt;222&gt; 240317 &lt;223&gt; Von Heijne matrix</pre>	
score 4 seq HHLLLSTLATIAG/NI	
<400> 599	
agaagactgg aactcagcaa gaaagtgatg aaaatgctct gagacataga aactctagac ggcagcatag aaatggaaga aaaataccca gccagatcca gctcagagcc aagaaaatgt acacaccaga tccccagcat tcccaattat cacaaaaggt gccttaattt ctatctacaa gacaacccta caatcctcac aggccctgag ctcagtatag aaagttttct ggagtccat atg gct gtt ttt ctc caa aag agg aaa cac aca atg aga cac cac cta  Met Ala Val Phe Leu Gln Lys Arg Lys His Thr Met Arg His His Leu  -25  -20  -15	60 120 180 239 287
ctc ctc agt aca ctg gct act ata gca ggc aac att tac aga Leu Leu Ser Thr Leu Ala Thr Ile Ala Gly Asn Ile Tyr Arg -10 -5 1	329
<210> 600 <211> 311 <212> DNA <213> Homo sapiens	
<220>	
<221> CDS <222> 169309	
<221> sig_peptide <222> 169246 <223> Von Heijne matrix	
score 4 seq PVAVEALLRAVFG/VV	
<400> 600 acagaggcgg caagactagg gtggaggaaa gctcaagggc catcgctggg tgcttcggtg	<b>CO</b>
gegggéagaa aegggaetgg cagtgeecae aegtgtgegt teteceegte egeeegaagg agetaeetgt geaeeetgee teeggetete etgageagag agateetg atg get gae Met Ala Asp	60 120 177
-25  Coa gaa gca ctc ccc tcc ctt gct ggg gac cca gtg gct gtg gaa gcc  Ser Glu Ala Leu Pro Ser Leu Ala Gly Asp Pro Val Ala Val Glu Ala  -20  -15 -10	225
ttg ctc cgg gcc gtg ttt ggg gtt gtt gtg gat gag gcc att cag aaa Leu Leu Arg Ala Val Phe Gly Val Val Val Asp Gly Ala Ile Gly Ive	273

```
- 5
 gga acc agt gtc tcc cag aag gtc tgc smg tgg aag ga
                                                                        311
 Gly Thr Ser Val Ser Gln Lys Val Cys Xaa Trp Lys
                      15
 <210> 601 /
 <211> 420
 <212> DNA
 <213> Homo sapiens
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 <221> CDS
 <222> 159..419
 <221> sig_peptide
 <222> 159..266
 <223> Von Heijne matrix
       score 4
       seq LAELPVSSPLCHA/VL
 <221> misc_feature
 <222> 365..366
 <223> n=a, g, c or t
<400> 601
ctaagccttt tctaccctct tctcaaagta gagccgaata tgattcagag gagagtctgg
                                                                         60
gaagtgatga tgatgacaat gatgatgatg atgatgtttt agcatcagat ttccatctcc
                                                                        120
aggaacattc taattcaaat tcatatagtt ggtccttg atg cgg ttg gcg atg gtg
                                                                        176
                                           Met Arg Leu Ala Met Val
                                                -35
caa ttg gtg ctc aac aat ttg aag act ttt tat ccc ttc gca gat cat
                                                                       224
Gln Leu Val Leu Asn Asn Leu Lys Thr Phe Tyr Pro Phe Ala Asp His
                     -25
                                         -20
gat ctt gca gag ctt cca gtt agt tca cct ctt tgt cat gcg gtt cta
                                                                       272
Asp Leu Ala Glu Leu Pro Val Ser Ser Pro Leu Cys His Ala Val Leu
                 -10
aaa act ctt caa tgt tgg gaa caa gtt ctt ctc cga cga ctt gaa atc
                                                                       320
Lys Thr Leu Gln Cys Trp Glu Gln Val Leu Leu Arg Arg Leu Glu Ile
cat ggt ggg cca cct caa aat tat atc gca agt cat acc gcc gan nag
                                                                       368
His Gly Gly Pro Pro Gln Asn Tyr Ile Ala Ser His Thr Ala Xaa Xaa
agt ttg tct gca ggt cct gca att ctt cgc cac aaa gct tta ctg gaa
                                                                       416
Ser Leu Ser Ala Gly Pro Ala Ile Leu Arg His Lys Ala Leu Leu Glu
                    40
                                                              50
cct a
                                                                       420
Pro
<210> 602
<211> 463
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 311..463
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<222> 311..370
<223> Von Heijne matrix
     score 4
     seq LFILXYFXXYTLS/SG
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<221> misc\_feature

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<222> 353..354
 <223> n=a, g, c or t
 <400> 602
 tggcaaagac aaagagttga aacttatatg gcagaatcag agctcacaat ggtgctgggc
                                                                      60
 atttggggtt ttgagtcttc tctgaagatc tttgacatct ttagctttat tctacaggcc
                                                                     120
acggggaact actggatatt tgaaagaagg aatttatctg tctatcttct atttatctat
                                                                     180
ctgtaatcta tcatctaatc taggaaatga tagatctagg aagatgatag ctagataaat
                                                                     240
300
taatttaaaa atg ttt aaa tta ttt tta ttt tta ttt att tta ttw tat
                                                                     349
           Met Phe Lys Leu Phe Leu Phe Leu Phe Ile Leu Xaa Tyr
          -20
                               -15
ttc nng vat tac act tta agt tct ggg ata tat gtg cag aat gtg cag
                                                                    397
Phe Xaa Xaa Tyr Thr Leu Ser Ser Gly Ile Tyr Val Gln Asn Val Gln
gtt tgt tac ata ggt ata cac atg cca tgg tgg ttt gct gca ccc atg
                                                                    445
Val Cys Tyr Ile Gly Ile His Met Pro Trp Trp Phe Ala Ala Pro Met
aac ctg tca tct gca cta
                                                                    463
Asn Leu Ser Ser Ala Leu
<210> 603
<211> 269
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 182..268
<221> sig_peptide
<222> 182..244
<223> Von Heijne matrix
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      seq LIPLLSEILYALA/NI
<400> 603
tgtttacaaa agtatcttga atttgataga gcttatgttg agaaataatt tttaatcttt
                                                                     60
taatteeatt titeeatgaa ettittigaag teecegtata eataettitt eatggigaga
                                                                    120
acacttataa tctactgtca gcaattttca aatataaaat atattattaa ctgtagtcac
                                                                    180
c atg ata tac agt aga tot ott gaa ott att oot ott ttg tot gaa att
                                                                    229
 Met Ile Tyr Ser Arg Ser Leu Glu Leu Ile Pro Leu Leu Ser Glu Ile
      -20
                         -15
ttg tat gct ttg gcc aac atc tcc cca atc ccc cag acg g
                                                                    269
Leu Tyr Ala Leu Ala Asn Ile Ser Pro Ile Pro Gln Thr
<210> 604
<211> 351
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 297..350
<221> sig_peptide
<222> 297..344
<223> Von Heijne matrix
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<222> 174

<223> n=a, g, c or t

score 4
seq VIFYFVLFLGIMT/QR

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aagaacatta tattttcaaa tggaataata ataccatcag tgaaataaat gttaaaattt
                                                                         60
 ttagggcaga gattaatgcc caccagaaag gtaactttga tgagggtagc aagcatgctt
 tcactgaaaa gtatttttt ttcctctttt caagattctc ataattataa cccataaaac
 taagttagac ttgtttctta tgtgcattta tgatttaatt aacgagagta cactttgtat
                                                                        240
 gacaaaatgc aattttaagg taaacactat ggagaataat ttcttttcct agtgaa atg
                                                                        299
 gtg cac gtt ata ttt tat ttt gtt tta ttt cta ggg ata atg aca cag
                                                                        347
 Val His Val Ile Phe Tyr Phe Val Leu Phe Leu Gly Ile Met Thr Gln
 -15
                     -10
 cgg g
                                                                        351
Arg
 <210> 605
 <211> 195
 <212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 37..195
<221> sig_peptide
<222> 37..111
<223> Von Heijne matrix
      score 4
      seq LIYFFQLHSCCHD/KV
agtgaagaat ctaagkccag agaggtggta gttaac atg cac aaa ttc ttt aga
                                                                        54
                                         Met His Lys Phe Phe Arg
                                         -25
cat ttc tat tca gat ttt ctg att tat ttc ttt cag ctc cat tca tgt
                                                                       102
His Phe Tyr Ser Asp Phe Leu Ile Tyr Phe Phe Gln Leu His Ser Cys
                -15
                                     -10
tgt cac gat aaa gtr act gcm cra agg gcc tat rtt cac tac agc agc
                                                                       150
Cys His Asp Lys Val Thr Ala Xaa Arg Ala Tyr Xaa His Tyr Ser Ser
            1
ctc tta act cct tac ctc tct cag cac ccc tgc ccc cat ccc ggg
                                                                       195
Leu Leu Thr Pro Tyr Leu Ser Gln His Pro Cys Pro His Pro Gly
    15
                        20
<210> 606
<211> 426
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 63..425
<221> sig_peptide
<222> 63..140
<223> Von Heijne matrix
      score 4
      seq LLRELRYLSAATG/HP
<221> misc_feature
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<400> 606	
ggaggagggg ttttcagggt cgtaggacgc cgttgggcac cacgctcgga gaagacagga	60
ca atg gcg gcc tta ggg tcc ccg tcg cac act ttt cga gga ctt ctg	107
Met Ala Ala Leu Gly Ser Pro Ser His Thr Phe Arg Gly Leu Leu -25 -20 -15	
cgg gag ttg cgc tac ctg agc gcg gcc acc ggc cac cct atc gcg aca	155
Arg Glu Leu Arg Tyr Leu Ser Ala Ala Thr Gly His Pro Ile Ala Thr	
-10 -5 1 5	
ccg cgg cct atc ggt acc ntt gtg aag gct ttc cgt gca cat cgg gtc Pro Arg Pro Ile Gly Thr Xaa Val Lys Ala Phe Arg Ala His Arg Val	203
10 15 20	
acc agt gaa aag ttg tgc aga gcc caa cat gag ctt cat ttc caa gct	251
Thr Ser Glu Lys Leu Cys Arg Ala Gln His Glu Leu His Phe Gln Ala	
25 30 35	
gcc acc tat ctc tgc ctc ctg cgt asa tcc gga aac atg tgg ccc tac Ala Thr Tyr Leu Cys Leu Leu Arg Xaa Ser Gly Asn Met Trp Pro Tyr	299
40 45 50	
atc agg aat ttc atg gca agg gtg agc gct cgg tgg agg agt ctg ctg	347
Ile Arg Asn Phe Met Ala Arg Val Ser Ala Arg Trp Arg Ser Leu Leu'	
55 60 65 get tgg tgg gtc tca agt tgc ccc atc agc ctg gag gga agg get ggg	305
Ala Trp Trp Val Ser Ser Cys Pro Ile Ser Leu Glu Gly Arg Ala Gly	.395
70 75 80 85	
age cat gaa cat gga gaa tat eet tgg atg e	426
Ser His Glu His Gly Glu Tyr Pro Trp Met 90 95	
30	
<210> 607	
<211> 161	
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<220>	
<221> CDS	
<222> 71160	
<221> sig_peptide	·, ·
<222> 71154	•
<223> Von Heijne matrix	
score 4 seq VSLFLLVVLYHYA/AV	
bed contract through	
<400> 607	
agttccggtc caggtctctg acttcgggct tgttcgctgg tggcgtcgga gccgagccgg	60
actggtcagg atg atc acg gac gtg cag ctc gcc atc ttc gcc aac atg Met Ile Thr Asp Val Gln Leu Ala Ile Phe Ala Asn Met	109
-25 -20	
ctg ggc gtg tcg ctc ttc ttg ctt gtc gtt ctc tat cac tac gcg gcc	157
Leu Gly Val Ser Leu Phe Leu Leu Val Val Leu Tyr His Tyr Ala Ala	
-15 -5 1	
gtg g Val	161
<b>***</b>	
<210> 608	
<211> 357	
<212> DNA <213> Homo sapiens	
(\$13) Homo aghtena	
<220>	
<221> CDS	
<222> 283357	

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<221> sig_peptide
 <222> 283..336
 <223> Von Heijne matrix
       score 4
       seq LSFLCSLSQNALN/IS
 <400> 608
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                                                                        60
tggcaggatt actatagtcc ccccaacaag ctctaccama gaagataata gaacttattg
                                                                       120
agcttaaatg aattatagga magttcctga aaagtccaar gtaaatgtga agagaacccg
                                                                       180
attetettaa eeteacecaa eecageaett gatteteeet tgttteetgg tttteataca
                                                                       240
cacactggga aaggamaagg aagaagaaac aaggatgtcg tt atg gct gaa gga
                                                                       294
                                                 Met Ala Glu Gly
                                                             -15
gct ttg agc ttc ctt tgc tct tta tcg caa aat gca ttg aat att tcc
                                                                       342
Ala Leu Ser Phe Leu Cys Ser Leu Ser Gln Asn Ala Leu Asn Ile Ser
                 -10
                                     -5
ctc att tct cgt aag
                                                                       357
Leu Ile Ser Arg Lys
<210> 609
<211> 201
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 133..201
<221> sig_peptide
<222> 133..180
<223> Von Heijne matrix
      score 4
      seq SFLLCFTLVGTQL/RN
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                                                                        60
ctgaattgaa tttagctctg tttacggttt tcttttctgt gagcagaagt tcttaatgat
                                                                       120
tactgtagtc aa atg tat cca tct ttt ctt tta tgc ttc aca ctc gta ggg
                                                                       171
              Met Tyr Pro Ser Phe Leu Leu Cys Phe Thr Leu Val Gly
                  . -15
                                       -10
act cag tta aga aat tct tcc tta gcc atg
                                                                       201
Thr Gln Leu Arg Asn Ser Ser Leu Ala Met
<210> 610
<211> 281
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 223..279
<221> sig_peptide
<222> 223..267
<223> Von Heijne matrix
      score 4
     seq SCTVGCATASSWG/CT
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<400> 610

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accgccttcc cacatcggat cgcagggctc ccaaaatggc gagtgagact gcggggactc
                                                                         60
 gctgagcagc ggagggggag cgtgcagarm mgctgcggcc ctcacagtcc ggagcccggc
                                                                        120
 cgtgccgtgc cgtagggaac atgcactttt ccattcccga aaccgagtcc cgcagcgggg
                                                                        180
 acageggegg eteegeetac gtggeetata acatteaegt ga atg gag tee tge
                                                                        234
                                               . Met Glu Ser Cys
                                                 -15
 act gtc ggg tgc gct aca gcc agc tcc tgg ggc tgy acg agc agg gg
                                                                        281
 Thr Val Gly Cys Ala Thr Ala Ser Ser Trp Gly Cys Thr Ser Arg
 <210> 611
 <211> 241
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> CDS
 <222> 28..240
 <221> sig_peptide
 <222> 28..156
 <223> Von Heijne matrix
       score 4
       seq AAWCSLVLSFCRL/HK
 agetteeggg ttteetggge tactaeg atg geg atg agt tte gag tgg eeg tgg
                               Met Ala Met Ser Phe Glu Trp Pro Trp
                                            -40
 cag tat ege tte eca ece tte ttt acg tta caa eeg aat gtg gae act
                                                                       102
Gln Tyr Arg Phe Pro Pro Phe Phe Thr Leu Gln Pro Asn Val Asp Thr
                 -30
                                     -25
cgg cag aag cag ctg gcc gcc tgg tgc tcg ctg gtc ctg tcc ttc tgc
                                                                       150
Arg Gln Lys Gln Leu Ala Ala Trp Cys Ser Leu Val Leu Ser Phe Cys
            -15
                                 -10
cgc ctg cac aaa cag tcc agc atg acg gtg atg gaa gct cag gag agc
                                                                       198
Arg Leu His Lys Gln Ser Ser Met Thr Val Met Glu Ala Gln Glu Ser
ccg ctc ttc aac aac gtc aag cta cag cga aag ctt cct gtg g
                                                                       241
Pro Leu Phe Asn Asn Val Lys Leu Gln Arg Lys Leu Pro Val
<210> 612 .
<211> 176
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 106..174
<221> sig_peptide
<222> 106..147
<223> Von Heijne matrix
      score 3.9000009536743
      seq RLHVHSLSPFSFA/CL
<400> 612
aagageettg gaacatetet etgaagaata aaacaaatet tttetgeatg tataategat
                                                                       60
ataaatttga ttatattgta ctttttattt cgtgtgtgtg tgtac atg aga tta cat
                                                                      117
                                                   Met Arg Leu His
gta cat tee ett tet eee tit tee tit get tgt ete eet tit etg tee
                                                                      165
Val His Ser Leu Ser Pro Phe Ser Phe Ala Cys Leu Pro Phe Leu Ser
```

```
WO 99/53051
                                                                PCT/IB99/00712
                                       328
 -10
                      - 5
                                          1
 ccc ccg ctg gg
                                                                        176
 Pro Pro Leu
 <210> 613
 <211> 342
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> CDS
 <222> 258..341
 <221> sig_peptide
 <222> 258..335
 <223> Von Heijne matrix
      score 3.90000009536743
       seq RMCILQLLSAVLY/RF
 <400> 613
catttctatk aaaatacaaa tttaaggctg tagatttaat atgtagtatg ttcattrrgt
                                                                        60
tccaaataca ttctaatttc cactgtgatt tctwctttga ctcmtgaawt atttagvagg
                                                                        120
tgwttttgwh ttabdwattt ctgactgtat ggggattttc tagttagttt wctactctta
                                                                        180
atttgtcttc agagamaata ctccacaaga tttcagtctt tcaattttgt tgcaacttgc
                                                                       240
tacaaacttg gcctaac atg ttg cat ttt wta tat atg atc caw gtg tgc
                                                                       290
                    Met Leu His Phe Xaa Tyr Met Ile Xaa Val Cys
ttg gaa aga atg tgc att ctg caa ttg ttg agt gct gtg ttg tat aga
                                                                       338
Leu Glu Arg Met Cys Ile Leu Gln Leu Leu Ser Ala Val Leu Tyr Arg
-15
                     -10
ttt g
                                                                       342
Phe
<210> 614
<211> 154
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 48..152
<221> sig_peptide
<222> 48..137
<223> Von Heijne matrix
      score 3.90000009536743
      seq VGLLDTPLGAVSA/HH
<221> misc_feature
<222> 17
<223> n=a, g, c or t
<400> 614
agtcggagcg aaggventgg eggasagaae ggattgeagg gteagee atg tea tet
                                                                        56
                                                     Met Ser Ser
                                                     -30
gag cct ccc cca cca cca cag ccc ccc acc cat caa gct tca gtc ggg
                                                                       104.
Glu Pro Pro Pro Pro Gln Pro Pro Thr His Gln Ala Ser Val Gly
        -25
                            -20
ctg ctg gac acc ccc ctc gga gcc gtg agc gct cac cat ccc ctc tgc
                                                                       152
Leu Leu Asp Thr Pro Leu Gly Ala Val Ser Ala His His Pro Leu Cys
```

-10

-5

```
CC
                                                                       154
<210> 615
<211> 272
<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 185..271
<221> sig_peptide
<222> 185..244
<223> Von Heijne matrix
      score 3.90000009536743
      seg FLTSISFLALVLW/NV
<400> 615
caactataat agcttttaaa cttgtttctc tttccttttc cttcatttca gtccatctta
ttatctttga caaaataatt tctctgatgc ctgactgcct gcccccaac aacaaagctt
                                                                       120
ttattatact tcttaactaa tcaactatwm cyttacccat ctagccaaag tagactaccc
atat atg ttt ctt gac cat gtc agg ttt tta acc tcc ata tct ttt ctt
     Met Phe Leu Asp His Val Arg Phe Leu Thr Ser Ile Ser Phe Leu
     -20
                         -15
                                              -10
get etg gte etg tgg aat gte ttt etc.aac tet ace egt etg g
                                                                       272
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                                                                        53
                                       Met Arg Glu Lys Pro Gln .
cca gcg ctc ctg act tca agt gar ctg cct gcc ttg gcc tct caa ata
                                                                       101
Pro Ala Leu Leu Thr Ser Ser Glu Leu Pro Ala Leu Ala Ser Gln Ile
           . -10
                                -5
cat tgc cgc gtc c
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His Cys Arg Val
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 ccc cac aac cac ttg gag gga gat gct ttg ctg aga gtc cct gtc ctc
                                                                       106
 Pro His Asn His Leu Glu Gly Asp Ala Leu Leu Arg Val Pro Val Leu
                     -20
                                         -15
 tgc atc tgg aga gct tgg ctc aga gct gag gtg gga ggg agg gct cct
                                                                       154
 Cys Ile Trp Arg Ala Trp Leu Arg Ala Glu Val Gly Gly Arg Ala Pro
ctt cca ggt cgc atg gg
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Leu Pro Gly Arg Met
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                                                                       120
ctgtgaaata ctttaaatat gagttgttgg gaaagttaa atg aaa aat act ctt
                                                                       174
                                            Met Lys Asn Thr Leu
tat tat aat ttt tgt tta ttt tgg att ytc cta cct ccc cac aca tgc
                                                                       222
Tyr Tyr Asn Phe Cys Leu Phe Trp Ile Xaa Leu Pro Pro His Thr Cys
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                             -10
aca cac aca gac aca cat
                                                                       240
Thr His Thr Asp Thr His
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tgc tcg gga ccg ctt tcc ctc cgt tcc cct cgg ctt ccc cct ctc ttt Cys Ser Gly Pro Leu Ser Leu Arg Ser Pro Arg Leu Pro Pro Leu Phe -25 -20 -15	162
tgc act ttt ctt tcc ctt tct ttg cat ccc tgg ggg ggt ttc ttt ttg Cys Thr Phe Leu Ser Leu Ser Leu His Pro Trp Gly Gly Phe Phe Leu -10 -5 1	210
tgt gcc tgg att tct bkt ttc ctc ccg tgg gtg tgt gtg tgk gcg gg Cys Ala Trp Ile Ser Xaa Phe Leu Pro Trp Val Cys Val Xaa Ala 5 10 15	257
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tca aag act agg acc aat gat gga aaa att aca tat ccg cct ggg gtc Ser Lys Thr Arg Thr Asn Asp Gly Lys Ile Thr Tyr Pro Pro Gly Val -85 -80 -75	103
aag gaa ata tca gat aaa ata tct aaa gag gag atg gtg aga cga tta Lys Glu Ile Ser Asp Lys Ile Ser Lys Glu Glu Met Val Arg Arg Leu -70 -65 -60 -55	151
aag atg gtt gtg aaa act ttt atg gat atg gac cag gac tct gaa gaa Lys Met Val Val Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Glu -50 -45 -40	199
Lys Met Val Val Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Glu -50 -45 -40 gaa aag gag ctt tat tta aac cta gct tta cat ctt gct tca gat ttt Glu Lys Glu Leu Tyr Leu Asn Leu Ala Leu His Leu Ala Ser Asp Phe -35 -30 -25	199 247
Lys Met Val Val Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Glu -50  gaa aag gag ctt tat tta aac cta gct tta cat ctt gct tca gat ttt Glu Lys Glu Leu Tyr Leu Asn Leu Ala Leu His Leu Ala Ser Asp Phe -35  ttt ctc aag cat cct gat aaa gat gtt cgc tta ctg gta gcc tgc Phe Leu Lys His Pro Asp Lys Asp Val Arg Leu Leu Val Ala Cys Cys -20  -15  -40  -40  -40  -40  -40  -40  -40  -4	
Lys Met Val Val Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Glu -50 -45  gaa aag gag ctt tat tta aac cta gct tta cat ctt gct tca gat ttt Glu Lys Glu Leu Tyr Leu Asn Leu Ala Leu His Leu Ala Ser Asp Phe -35 -30 -25  ttt ctc aag cat cct gat aaa gat gtt cgc tta ctg gta gcc tgc Phe Leu Lys His Pro Asp Lys Asp Val Arg Leu Leu Val Ala Cys Cys -20 -15  ctt gct gat att ttc agg att tat gct cct gaa gct cct tac aca tcc Leu Ala Asp Ile Phe Arg Ile Tyr Ala Pro Glu Ala Pro Tyr Thr Ser	247
Lys Met Val       Val       Lys Thr       Phe       Met       Asp       Met       Asp       Gln       Asp       Ser       Glu       Glu       Glu       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40       -40	247 295
Lys Met Val Val Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Glu -50  gaa aag gag ctt tat tta aac cta gct tta cat ctt gct tca gat ttt Glu Lys Glu Leu Tyr Leu Asn Leu Ala Leu His Leu Ala Ser Asp Phe -35  ttt ctc aag cat cct gat aaa gat gtt cgc tta ctg gta gcc tgc tgc Phe Leu Lys His Pro Asp Lys Asp Val Arg Leu Leu Val Ala Cys Cys -20  ctt gct gat att ttc agg att tat gct cct gaa gct cct tac aca tcc Leu Ala Asp Ile Phe Arg Ile Tyr Ala Pro Glu Ala Pro Tyr Thr Ser -5  cct aag gg	247 295 343
Lys Met Val Val Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Glu -50  gaa aag gag ctt tat tta aac cta gct tta cat ctt gct tca gat ttt Glu Lys Glu Leu Tyr Leu Asn Leu Ala Leu His Leu Ala Ser Asp Phe -35  ttt ctc aag cat cct gat aaa gat gtt cgc tta ctg gta gcc tgc tgc Phe Leu Lys His Pro Asp Lys Asp Val Arg Leu Leu Val Ala Cys Cys -20  ctt gct gat att ttc agg att tat gct cct gaa gct cct tac aca tcc Leu Ala Asp Ile Phe Arg Ile Tyr Ala Pro Glu Ala Pro Tyr Thr Ser -5  cct aag gg Pro Lys  <210> 621 <211> 118 <212> DNA	247 295 343

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gatti	tcactt	attt	taat	ta t	:++++	tgat	ra et	-ayyu	.c.ac	. aag	cago	tgt	accc	tggtt	: C	60
tttt	tagttt	ttat	tttc	ct a	cacc	atac	c at	agta	gaca	tat	tact	att	gyat	tttat	JL.	120
tttt	ttaaaa	aatt	cact	tg t	ttt	ctcc	ia da	attt	ataa	cta	attt	tta	tatt	atact	a G	180 240
cataa	attcag	taat	ttca	cac	atta	acaa	c at	ccac	aato	atq	taaa	gat	gagt	tttct	-9 :a	300
gctto	ctgaaa	tgtt	ctga	99 a	tgta	attt	t tt	aata	agag	gaa	atq	tnn	tct	cac		355
										_			Ser		•	
													-25			
aga d	ta ttt	999	tgt	ttt	cca	agt	gac	: ttg	tca	cga	atg	gtt	ttg	ctc	•	403
Arg I	Leu Phe	GIY	Cys	Phe	Pro	Ser			Ser	Arg	Met			Leu		
tot -	gt gca	-20		act		~~~	-15					-10				
Ser S	er Ala	Len	Len	Ser	Thr	Glu	aac	Ca					•			432
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agagg		gaaaa catta	iacat igaag	g ta ja ga	aacat acctt	gtaa	ate	g cg	c cca	a tca	a cat	te	t tca	caga gcc Ala	•	60 114
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Phe	Ala	Asp	cgg Arg 50	Leu	Arg	Ala	Val	Asp 55	Thr	Asp	Gly	Val	Glu 60	Pro	Met	243
Glu	Ser	Val 65	ctg Leu	Glu	Asp	Arg	Cys 70	Leu	Tyr	Leu	Arg	Ser 75	Asp	Asn	Val	291
Val	Glu 80	Gly	aac Asn	Cys	Ala	Asp 85	Glu	Leu	Leu	Gln	Asn 90	Ser	His	cgc Arg	gtc ' Val	339
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ccc ( Pro (	Gly	gaa Glu -70	cgt Arg	ctg Leu	tgt Cys	Asn	ttg Leu -65	gag	gag	ggc Gly	agc Ser	ccg Pro -60	qqc	agc	ggc Gly	101
Thr 1	tac Tyr -55	acc Thr	cgc Arg 1	cac His	Gly	tac Tyr -50	atc Ile	ttt Phe	tcg Ser	tcg Ser	ctw Leu -45	rcc	ggc Gly	tgt Cys	ctg Leu	149
atg a Met I -40	aag Lys	agc Ser	agc ( Ser (	Glu	aat Asn -35	ggc ( Gly .	gcg Ala	ctt Leu	cca Pro	gtg Val -30	gtg	tct Ser	gta Val	gtg Val	aga Arg -25	197
gaa a Glu 1	ca (	gag Glu	tcc ( Ser (	cag : Gln : -20	tta Leu	ctg ( Leu )	cca Pro	Asp	gtg Val -15	gga Gly	gct Ala	att Ile	gta Val	acc Thr -10	tat	245
ag t	er 1	Leu .	gca t Ala s -5	ca a Ser	att (	cac q His A	gct Ala :	ttg	cca	a				-•		276

335

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       seq RLLVARLHMASLA/RR
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cgggtgagat caaattggga atgctttcat aatgaacgtc aaccagtcag ttccacctgt
                                                                        120
gccaccattt gggcagcccc agcccatcta cccagggtat catcagtcca gct atg
                                                                        176
                                                             Met
                                                             -60
gtg ggc aat cag ggt cca cag ccc ccg cca ttc cct atg gag cct aca
                                                                       224
Val Gly Asn Gln Gly Pro Gln Pro Pro Pro Phe Pro Met Glu Pro Thr
                 -55
                                     -50
atg gcc cag tac cag gct atc agc aaa cac ctc ccc aag gta tgt caa
                                                                       272
Met Ala Gln Tyr Gln Ala Ile Ser Lys His Leu Pro Lys Val Cys Gln
             -40
                                 -35
                                                      -30
gag ccc cac ctt cct cgg ggg cac ctc cag cct caa cag cac agg ctc
                                                                       320
Glu Pro His Leu Pro Arg Gly His Leu Gln Pro Gln Gln His Arg Leu
        -25
                             -20
                                                 -15
ctt gtg gcc agg ctg cat atg gcc agt ttg gca agg aga tgt aca gaa
                                                                       368
Leu Val Ala Arg Leu His Met Ala Ser Leu Ala Arg Arg Cys Thr Glu
                        -5
tgg gcc aag ctc cac tgt tca gat gca agg ctg ccc tgg gtc tca gc
                                                                       415
Trp Ala Lys Leu His Cys Ser Asp Ala Arg Leu Pro Trp Val Ser
                10
                                     15
<210> 628
<211> 318
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<400> 628

<223> n=a, g, c or t

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gtg agt gtt aca gtt ctt aaa gat ggt gtg gct gga gtt tgt ttc ttc Val Ser Val Thr Val Leu Lys Asp Gly Val Ala Gly Val Cys Phe Phe -20 -15 -10	282
aga cgt tca gat gcg tct gaa gtt tct tcc ttc tgg Arg Arg Ser Asp Ala Ser Glu Val Ser Ser Phe Trp -5 5	318
<210> 629 <211> 170 <212> DNA <213> Homo sapiens	
<220> <221> CDS <222> 29169	
<pre>&lt;221&gt; sig_peptide &lt;222&gt; 29157 &lt;223&gt; Von Heijne matrix</pre>	:
score 3.90000009536743 seq KCLFLSFAHFLMG/RT <400> 629	•
cattttgact ggtgtaagat gatatctc atg gtg gtt ttg att tgc ctt tct Met Val Val Leu Ile Cys Leu Ser ~40	52
ctc atg atc agt aat act gag ctt ttt ttc ata cgc ttc ttg act gca Leu Met Ile Ser Asn Thr Glu Leu Phe Phe Ile Arg Phe Leu Thr Ala -35 -25 -20 tgt atg cct tct ttt gaa aag tgt ctg ttc tta tct ttt gcc cac ttc	100
Cys Met Pro Ser Phe Glu Lys Cys Leu Phe Leu Ser Phe Ala His Phe -15 -10 -5 ttg atg gga aga acc cac cgt g	148
Leu Met Gly Arg Thr His Arg	.170
<210> 630 <211> 196 <212> DNA <213> Homo sapiens	•
<220> <221> CDS <222> 87194	
221> sig_peptide 222> 87152 223> Von Heijne matrix score 3.90000009536743	,
seq SLLSDILFANIFS/HS	e.
accatttgta tatatttgav aaatatctat tcaaatacat tgcctgcttt aaaatactgt attggtctt tttatcattg gattgt atg agt tct tta tat att ttg gat att Met Ser Ser Leu Tyr Ile Leu Asp Ile -20 -15	60 113
gt ctc tta tca gat ata tta ttt gca aat att ttc tcc cat tct tgg er Leu Leu Ser Asp Ile Leu Phe Ala Asn Ile Phe Ser His Ser Trp	161

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-10
                                                      1
 gac gtc ttt cca ctt tct ttt ctt ttc ttt tct tt
                                                                       196
 Asp Val Phe Pro Leu Ser Phe Leu Phe Phe Ser
                         10
<210> 631
 <211> 339
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> CDS
 <222> 53..337
<221> sig_peptide
<222> 53..304
<223> Von Heijne matrix
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                                                                        58
caa gga gct cgc ggc tgg cac aga gag cca ggc ctt ggt ctc cgc cac
                                                                       106
Gln Gly Ala Arg Gly Trp His Arg Glu Pro Gly Leu Gly Leu Arg His
        -80
                           -75
tee eeg aga aga ett teg ggt geg etg eac ete gaa geg gge tgt gac
                                                                       154
Ser Pro Arg Arg Leu Ser Gly Ala Leu His Leu Glu Ala Gly Cys Asp
                        -60
cga aat gct aca act gtg cgg ccg ctt cgt gca aaa shc ggg gac gct
                                                                       202
Arg Asn Ala Thr Thr Val Arg Pro Leu Arg Ala Lys Xaa Gly Asp Ala
                    -45
                                        -40
ctg ccg gag gag att cgg gag ccc gct ctg cga gat gcg cag tgg gta
                                                                       250
Leu Pro Glu Glu Ile Arg Glu Pro Ala Leu Arg Asp Ala Gln Trp Val
                -30
                                    -25
egg gac dag tha ged agt tet tha etc atc atc etc tha eec aac acc
                                                                      298
Arg Asp Gln Leu Ala Ser Ser Leu Leu Ile Ile Leu Leu Pro Asn Thr
            -15
                                -10
cag gat ctt agg att cag aaa gat ccc aca cca ggc ccg gg
                                                                      339
Gln Asp Leu Arg Ile Gln Lys Asp Pro Thr Pro Gly Pro
<210> 632
<211> 433
<212> DNA
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<220>
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<222> 171..431
<221> sig_peptide
<222> 171..314
<223> Von Heijne matrix
     score 3.79999995231628
     seq NSLLLLCLYIYP/HS
<221> misc feature
<222> 376..377
<223> n=a, g, c or t
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actct agata tggat	acat	gg t	caga	gacc	ag g	agaa	aata	t ga	ataa	cttt	ctt	ctaa	aca	agga		t g	60 120 176
Lys A	aga Arg -45	aag Lys	atc Ile	agt Ser	gtg Val	tgt Cys -40	Gln	caa Gln	act Thr	tgg Trp	gcc Ala -35	Leu	tta Leu	tgc	aaq (		224
aac t Asn P -30	he	Leu	Lys	Lys	Trp -25	Arg	Met	Lys	Arg	Glu -20	Ser	Leu	Met	Glu	Trp -15		272
ctg a Leu A	lsn :	Ser	Leu	Leu -10	Leu	Leu	Leu	Cys	Leu -5	Tyr	Ile	Tyr	Pro	His 1	Ser		320
cat c His G	in '	Val 5	Asn .	Xaa	Xaa	Ser	Ser 10	Leu	Leu	Thr	Met	Asp 15	Leu	Gly	Arg		368
gta g Val A 2	at : sp :	rnn Xaa	tkt Xaa	aat Asn	gaa Glu	tcc Ser 25	aga Arg	ttt Phe	tct Ser	gtt Val	gta Val 30	tac Tyr	aca Thr	Pro	gtc Val		416
acc a Thr A 35					<b>gg</b>	•									. (		433
<210>							•							•			
<211><212><213>	DN/	Α.	apie	ns													•
<220>																	
<221>												•					
<222>	54.	15	2		•												
<221>		_		e					-								
<223>	Von	He.	ijne 3.79	mat 9999 XLLK	9523		I					•				•	
<400>	633	ì															•
cagtta			atct	gtgt	g tg	agca	agtt	tat	atgt	gta	caca	tgtt	tg d	CCC &	atq	•	56
tgt ac												_	_		1et -30		104
Cys Tì	hr C	ys I	Leu (	Cys ' -25	Val	Cys	Leu	Tyr	Met -20	Tyr	Asn	Met	Gln	Phe	Leu		104
kyt tt Xaa Pl	tt g he V	al E	Phe '	yal (	tgc ( Cys )	gww Xaa	Leu	cta Leu -5	aag Lys	tgt Cys	atg Met	agt Ser	gtg Val 1	Pro	ttg Leu		152
tg																	154
<210>																	
<211><212>																	
<213>			pier	ns													
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<221><222>			)							•							
<221>				<b>e</b>													
<222>	34.	.126	i														
<223>			-	matı 99999		1628					,						

## seq PVCLLVLGMAGSG/KT

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<210> 636 <211> 172 <212> DNA <213> Homo sapiens

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 <222> 38..109
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                                                                        .55
                                          Met Gly Phe Leu Gly Ser
 ccc aga cag aga aac tca atg tgt ttg ctt tta gac gtc agc tct rcc
                                                                       103
 Pro Arg Gln Arg Asn Ser Met Cys Leu Leu Leu Asp Val Ser Ser Xaa
             -15
                                 -10
 aag agc aca gat aat tth cya rtc gww wtt ttg att att tat tat ctg
                                                                       151
Lys Ser Thr Asp Asn Xaa Xaa Xaa Xaa Leu Ile Ile Tyr Tyr Leu
                       5
 att acc aga aaa ggg cca ggg
                                                                       172
 Ile Thr Arg Lys Gly Pro Gly
<210> 637
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<212> DNA
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<222> 100..252
<221> sig_peptide .
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      seq FNIFLAAPSPVWQ/PQ
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acaagcactg caatgcagca accattgacc taactatgct teetteteca ggtcatetea
                                                                       60
agcagacccc tcactctgaa gcccccggat ccaagcagg atg agc tgc caa mct
                                                                      114
                                     Met Ser Cys Gln Xaa
mag ctt gct cdg acc ttg act tgg ctc atg atc cgt gga aga cat ccc
                                                                      162
Xaa Leu Ala Xaa Thr Leu Thr Trp Leu Met Ile Arg Gly Arg His Pro
            -35
                                -30
                                                    -25
tac ctg acc cgt cga tca gcc cga aac ttc aac atc ttt ttg gca gct
Tyr Leu Thr Arg Arg Ser Ala Arg Asn Phe Asn Ile Phe Leu Ala Ala
        -20
                            -15
                                                -10
ccg tcc cca gtt tgg cag cct cag agg acc cgc cga ccc cag k
                                                                      253
Pro Ser Pro Val Trp Gln Pro Gln Arg Thr Arg Arg Pro Gln
   -5
<210> 638
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<212> DNA
<213> Homo sapiens
<220>
<221> CDS
<222> 32..184
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       seq FHQMALXPGTSRA/QA
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                                                                         52
                                     Met Cys Pro Ala Trp Leu Pro
 tgt tgg acg gca cag acg gaa cat ctc gat cgt tac agg aag ttc cac
                                                                        100
 Cys Trp Thr Ala Gln Thr Glu His Leu Asp Arg Tyr Arg Lys Phe His
         -25
                             -20
 cag atg gcg ctg tyt cca ggg aca tct agg gca cag gcc tta ctt tat
                                                                        148
 Gln Met Ala Leu Xaa Pro Gly Thr Ser Arg Ala Gln Ala Leu Leu Tyr
                         -5
 aac gaa gtc cta gag aga ttt atg ttc acc cgg ctg c
                                                                       185
 Asn Glu Val Leu Glu Arg Phe Met Phe Thr Arg Leu
                 10
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<222> 73..204
<221> sig_peptide
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      seq RICTFLLPSHSTS/GP
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                                                                        60
taggettigt tg atg aat gte atg aag aga ata tgt ace tit etg tig eet
                                                                       111
              Met Asn Val Met Lys Arg Ile Cys Thr Phe Leu Leu Pro
                                               -10
tea eac tet acc tet gge eet etg tge tgt tea aat gee eat ett eet
                                                                       159
Ser His Ser Thr Ser Gly Pro Leu Cys Cys Ser Asn Ala His Leu Pro
-5
                                                         10
get acc tee tet acc ttg aaa cat tge agg get tgg agg gaa geg bv
                                                                       206
Ala Thr Ser Ser Thr Leu Lys His Cys Arg Ala Trp Arg Glu Ala
            15
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      seq SLATLPFLSTVVT/DK
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<221> misc\_feature

60

120

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eteateagga ecagtetgae tgeacetgea teettagete agageateee eggageatet

				343			
taagagetga g cetteceeet d ceagagetgt g	tccctgaco	ct agagct	ctac age	ctgctgcc	tcggtactg	t ccgctggata a ccgagggttc a cgac atg	180 240 297
gct gag atc						Met	
Ala Glu Ile -35	Thr Asn	Ile Arg	Pro Ser -30	Phe Asp	Val Ser P -25	ro Val Val	345
gcc ggc ctc Ala Gly Leu -20	atc ggg Ile Gly	gcc tct ( Ala Ser '	gtg ctg Val Leu	gtg gtg Val Val	tgt gtc t Cys Val S -10	cg gtg acc er Val Thr	393
gtc ttt gtc Val Phe Val -5	tgg tca Trp Ser	tgc tgc ( Cys Cys )	crc cag Xaa Gln	cag gca Gln Ala 5	gag aag a Glu Lys L	ag cac aag ys His Lys 10	441
aac cca cca Asn Pro Pro						er	483
<210> 642 <211> 309							•
<212> DNA <213> Homo s	apiens			•			
<220> <221> CDS <222> 2353	09				. *		`;
	79 ijne mat 3.79 <b>9</b> 999	95231628					
seq 11 <400> 642	TMLILLIH	EHG/1F					
attratctat g aatatgtttt g ctttggctgw t tctgtgaaaa g	aagtcagg ttgggttc	t agtgtga w wttwtgg	itgc ctc jttc cat	cagattt acaaatt	gttctttttg ttaggattat	gtcaggattg tttttctatg	60 120 180 237
gtc att tta a Val Ile Leu !			eu Leu			t att ttc	285
ttt tca ctt 9 Phe Ser Leu 1 5		Val Leu P				·	309
<210> 643 <211> 245 <212> DNA							•
<213> Homo sa	apiens						-
<220> <221> CDS <222> 14724	15	·					
	3	5231628					

<222> 61

<223> n=a, g, c or t

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yacgcacco sactcagcat aacctgctca cacaatcaca cacacaatca cacacacct	120
cocagtaca goccactoag acacac atg tto toa cac aat cac toa tac aca '	173
Met Phe Ser His Asn His Ser Tyr Thr	
-25	
ac aca cca cag cac age ccg ctc aca cac aca cac aca tgc acc cca	221
yr Thr Pro Gln His Ser Pro Leu Thr His Thr His Thr Cys Thr Pro	
20 -15 -10 -5	
ec age aca get cae eca ege ggg	249
Pro Ser Thr Ala His Pro Arg Gly	
1	
210> 644	
211> 211	
212> DNA	
213> Homo sapiens	
220>	
221> CDS	
222> 144209	
221> sig_peptide	
222> 144188	
223> Von Heijne matrix	
score 3.79999995231628	
seq XMILLCFLAVSNF/NK	
400. 644	
400> 644	
tactettte tacattetge teegetttag etgegagagt ttaccaacte aaatetggee	
tactettte tacattetge teegetttag etgegagagt ttaccaacte aaatetggee aageetgga cagtetagat aaggaagegg atcacaaaaa caaattggte tgtgtgtgtg	120
tactettte tacattetge teegetttag etgegagagt ttaccaacte aaatetggee aageetgga cagtetagat aaggaagegg atcacaaaaa caaattggte tgtgtgtgt gegtgegtg cacgegeetg tgt atg ttt kat atg att tta ett tgt ttt ttg	60 120 173
tactctttc tacattctgc tccgctttag ctgcgagagt ttaccaactc aaatctggcc aagcctgga cagtctagat aaggaagcgg atcacaaaaa caaattggtc tgtgtgtg gcgtgcgtg cacgcgcctg tgt atg ttt kat atg att tta ctt tgt ttt ttg Met Phe Xaa Met Ile Leu Leu Cys Phe Leu	120
tactctttc tacattctgc tccgctttag ctgcgagagt ttaccaactc aaatctggcc aagcctgga cagtctagat aaggaagcgg atcacaaaaa caaattggtc tgtgtgtg gcgtgcgtg cacgcgcctg tgt atg ttt kat atg att tta ctt tgt ttt ttg Met Phe Xaa Met Ile Leu Leu Cys Phe Leu -15	120 173
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tactctttc tacattctgc tccgctttag ctgcgagagt ttaccaactc aaatctggcc aagcctgga cagtctagat aaggaagcgg atcacaaaaa caaattggtc tgtgtgtg gcgtgcgtg cacgcgcctg tgt atg ttt kat atg att tta ctt tgt ttt ttg Met Phe Xaa Met Ile Leu Leu Cys Phe Leu -15	120 173
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aatttcdgaa caactatgaa tacaaaaaga attttaaaat cccagtcctg cctagaaagg
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                   Met Val Ala Leu Gly Gln Leu Ala Xaa Leu Pro
ggc nbc tdc cat ggg ggc ctt tct gca gtg act gtg gtt ctt ccc att
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Gly Xaa Xaa His Gly Gly Leu Ser Ala Val Thr Val Val Leu Pro Ile
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Leu Leu Cys
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                                                                       110
                   Met Pro Val Ser Phe Val Cys Leu Leu Phe Arg
                   -15
                                        -10
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                                                      -25
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Asp Ser Leu Leu Gly Gly Arg Gly Ser Leu Pro Leu Leu Pro Ala
                             -15
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                                                                       151
His His Gly Arg His Gly Ser Gly Leu Pro Ala Pro Asp Pro Ser Pro
ccc cca gga cca gct gtt cca ggg ccc tgg ccc tgc cag gat gag ctg
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Pro Pro Gly Pro Ala Val Pro Gly Pro Trp Pro Cys Gln Asp Glu Leu
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cca agc ctc agg cca gcc acc tcc cac cac ttt
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Pro Ser Leu Arg Pro Ala Thr Ser His His Phe
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    Met Ala Val Gly Gly Thr Ala Val Ile Thr Arg Arg Leu Leu Gly
    -25
                        -20
                                             -15
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                                                                       96
Arg Ser Gly Phe Ser Phe Gln Val Ser Gly Trp Gly Trp Gly Glu Arg
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rei	1 Ale	a ni	s nı	s Pr -5	o ar	g Th	c tc r Se	a gg r Gl	a cag y Gl: 1	g aa n Ly	g cg s Ar	a gag g Gli	g cc u Pro 5	c ati	gct Ala	400
Pro	Ala	GI 10	g ct n Le	c ag u Se	c cc r Pr	99				•						, 419
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iie	ьец -70	ASI	СТА	Pne	Arg	-65	His	Ala	Thr	Asp	Ser -60	Val	Lys	Asn		105
мет -55	GIu	ser	мет	Asn	-50	Asp	Met	Val	Ile	Ile	Pro	Gly	Gly		Thr.	153
ser	GIN	Leu	GIN	-35	Leu	Asp	Val	Val	Val -30	Tyr	Lys	Pro	Leu	aat Asn -25	Asp	201
agt Ser	gtg Val	cgg Arg	gcc Ala -20	cag Gln	tac Tyr	tcc Ser	aac Asn	tgg Trp -15	ctt Leu	ctg Leu	gct Ala	ggg ggg	aac Asn -10	ctg Leu	gcg Ala	249
Leu	Ser	Pro	Thr	Gly	Asn	Ala	Lys 1	aag Lys	Pro	Pro	Leu 5	Gly	ctc Leu	ttt Phe	Leu	297
Glu 10	Trp	Val	Met	Val	Ala 15	Trp	Asn	Ser	Ile	Ser 20	Ser	Glu	Ser	atc Ile	Val	345
caa Gln	ggg Gly	whc Xaa	aaa Lys	gaa Glu 30	gtg Val	cca Pro	tat Tyr	ctc Leu	crg Xaa 35	caa Gln	ctt Leu	gga Gly	gga Gly	gga Gly 40	202	393
cga																306

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                                                                        108
       Met Ile Cys Thr Thr Val Tyr Ile Thr Met Ala Pro Tyr Cys
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cta tca aac tgt tta ctt thw caw agt tgg ggc ctg cat ttg tat aga
                                                                        156
Leu Ser Asn Cys Leu Leu Xaa Xaa Ser Trp Gly Leu His Leu Tyr Arg
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Phe Leu Ala Pro
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tottcatttc atg gtt tot ctc tgt gta gct gct tta ttt cct ctt cag
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	ta tat eu Tyr											,		•		197
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ttk gt Xaa Va	l Phe	kgt : Xaa : -10	ttt Phe	tkg Xaa	ttt Phe	ttg Leu	ara Xaa -5	cgg Arg	asy Xaa	ttg Leu	cyc Xaa	tkg Xaa 1	ycg Xaa	ccc Pro		159
agg ct Arg Le 5	g gag u Glu	tgc a Cys 1	aat Asn	ggm Gly	aar Lys 10	ayc Xaa	tcg Ser	gcy Ala	cac His	tgm Xaa 15	aac Asn	ctc Leu	cgc Arg	ctc Leu		20,7
ctg ag Leu Se 20	t yca a r Xaa a	agc a Ser A	aat Asn	tcy Ser 25	ctk Leu	gcc Ala	tca Ser	gcc Ala	ccc Pro 30	cga	ggg Gly					246
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	31300	) ijne 3.700	mat:	0476		!										
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388

411

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agt gaa att gca gaa atg gga gct ggt att cta gag gaa aaa aat tat

Ser Glu Ile Ala Glu Met Gly Ala Gly Ile Leu Glu Glu Lys Asn Tyr

10

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Gly Gln Gln Xaa His Cys Asn

ggv caa caa wat cac tgt aac ta

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                                                                       55
                                          Met Ser Leu Pro Pro Phe
                                          -30
ttc cac cct tct ccc gct ccc tct ctc gct ccc cct ccc tcc ctc ttt
                                                                      103
Phe His Pro Ser Pro Ala Pro Ser Leu Ala Pro Pro Pro Ser Leu Phe
                -20
                                    -15
ctt tcc ctc cct ccc tct ctt tct ccc cct cta ccc gcc cgg g
                                                                      146
Leu Ser Leu Pro Pro Ser Leu Ser Pro Pro Leu Pro Ala Arg
                                ī
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         Met Phe Phe Leu Cys Gly Phe Leu Tyr Leu Cys Phe Ile Ser
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Phe Phe Phe Phe
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aatgtaccac agtttgttta accattcacc cactgaagga cgtttggatt gtttctaagt

atg tt Met Pl -25 tgt at	ne L	eu I	Phe	Cys	Trp -20	g gag o Glu )	aaa Lys	a ago	cca Pro	aga Arg -15	atg Met	Cag Gln	ttg Leu	Leu	ggt Gly		179 227
Cys Me	t V	al I	Leu	Tyr -5	Asp	Cys	Phe	Ser	Phe	Lys	Lys	Leu	Pro 5	Gly	, ,		273
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	seq														. ,		
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cgt tt Arg Pho	e se 5	r Pr	ie v	aı (	Cys	Phe	Phe	His	Val	Phe	Tyr -5	Cys	Val	Phe	Cys		97
aac gt Asn Va 1	tc l Se	t to r Se	et t er L 5	eu I	ttc Phe	tcc Ser	tat Tyr	cag Gln	ttt Phe 10	ctt Leu	ctt Leu	cat His	ttc Phe	tgt Cys 15	gat Asp		145
gac t Asp	_														-		149
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	61	08 eiji 3.	ne n 7000	natr	4768				• .								
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at tct	ccc	aac	: tc	t aa	-30 aa t	ta c	gc a	atg d	gga a	Arg -25	aac t	itt 1	tc :	tca d	-20		99
sn Ser	Pro	Asn	. Se -1	r Ly 5	ys L	eu (	Sly N	iet (	3ly N -10	let C	Sly I	Phe 1	Phe S	Ser (	sly		
al Lys	Ser	Trp	Il	e G]	ly G	ly	,∽									1	.22

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                                         Met Ala Ser Xaa Val Pro
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gtg aag gac aag aaa ctt ctg gag gtc aaa ctg ggg gag ctg cca agc
                                                                       103
Val Lys Asp Lys Lys Leu Leu Glu Val Lys Leu Gly Glu Leu Pro Ser
                    -25
                                        . -20
tgg atc ttg atg cgg gac ttc agt cct agt ggc att ttc gga gcg ttt
                                                                       151
Trp Ile Leu Met Arg Asp Phe Ser Pro Ser Gly Ile Phe Gly Ala Phe
                -10
caa aga ggt tac tac cgg tac tac aac aag tac atc aat gtg aag aag
                                                                       199
Gln Arg Gly Tyr Tyr Arg Tyr Tyr Asn Lys Tyr Ile Asn Val Lys Lys
                            10
ggg agc atc tcg ggg att acc atg gtg ctg gca tgc tac gtg ctc ttt
                                                                       247
Gly Ser Ile Ser Gly Ile Thr Met Val Leu Ala Cys Tyr Val Leu Phe
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                                             30
age tac tee ttt tee tac aag cat etc aag cac gag teg gg
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Ser Tyr Ser Phe Ser Tyr Lys His Leu Lys His Glu Ser
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gctgagcctg aagctggact tgccggtg atg gtg ata tcg gcc ggg gca ctg
                                                                       112
                               Met Val Ile Ser Ala Gly Ala Leu
                                           ~15
ctg tgg atg gcg tgg gac ggc cag ctc agc cgc ccc gaa ggc gcc cqt
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Leu Trp Met Ala Trp Asp Gly Gln Leu Ser Arg Pro Glu Gly Ala Arg
-10
                    -5
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                                               Met Val His Cys
aat ctt gaa ctc ctg ggc tca agt tat aat ccc atc tca gcc tct cca
                                                                    103
Asn Leu Glu Leu Leu Gly Ser Ser Tyr Asn Pro Ile Ser Ala Ser Pro
                -10
                                    -5
gta gct agg act ata tca tgc ccc gct att gtg g
                                                                    137
Val Ala Arg Thr Ile Ser Cys Pro Ala Ile Val
                           10
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116
                                                      Met Leu
                                                                    164
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Gly Ser Gly Phe Lys Ala Glu Arg Leu Arg Val Asn Leu Arg Leu Val
                        -80
ata aat cgc ctt aaa cta ttg gag aaa aag aaa acg gaa ctg gcc cag
Ile Asn Arg Leu Lys Leu Leu Glu Lys Lys Lys Thr Glu Leu Ala Gln
                                       -60
                   -65
                                                                    260
aaa gca agg aag gag att gct gac tat ctg gct gct ggg aaa gat gaa
Lys Ala Arg Lys Glu Ile Ala Asp Tyr Leu Ala Ala Gly Lys Asp Glu
                                    -45
                -50
                                                                    308
cga get egg ate egt gtg gag eac att ate egg gaa gae tae ete gtg
Arg Ala Arg Ile Arg Val Glu His Ile Ile Arg Glu Asp Tyr Leu Val
            - 35
                                -30
gag gcc atg gag atc ctg gag ctg tac tgt gac ctg ctg ctg gct cgg
                                                                    356
Glu Ala Met Glu Ile Leu Glu Leu Tyr Cys Asp Leu Leu Leu Ala Arg
                            -15
                                                -10
                                                                    404
ttt ggc ctt atc cag tct atg aag gaa cta gat tct ggt ctg gct gaa
Phe Gly Leu Ile Gln Ser Met Lys Glu Leu Asp Ser Gly Leu Ala Glu
                                                                     452
tot gtg tot aca ttg atc tgg gct gct cct cga ctc cag tca gaa gtg
Ser Val Ser Thr Leu Ile Trp Ala Ala Pro Arg Leu Gln Ser Glu Val
                15
                                    20
gct gag ttg aaa ata gtt gct gat cag ctc tgt cca agt at
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Ala Glu Leu Lys Ile Val Ala Asp Gln Leu Cys Pro Ser

30		35		•
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gct cct gct tgg aga Ala Pro Ala Trp Arc -35	Xaa Leu Xaa	Thr Arg Arg	Leu Pro Met Gly -25	Ser
agg cac ggt gcc agg Arg His Gly Ala Ser -20	c ccg gcc tct Pro Ala Ser -15	gcc gtc tgg Ala Val Trp	tgt ctg tmc ctc Cys Leu Xaa Leu -10	aag 212 Lys
tta gtc cca gct ttg Leu Val Pro Ala Leu	tgc att agc Cys Ile Ser	ggg ctc acc Gly Leu Thr 5	ctc gga atc cag Leu Gly Ile Gln	gga 260 Gly 10
ttc Phe		_	,	263
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tat ttt aaa acc act Tyr Phe Lys Thr Thr -30	Thr Xaa Xaa	His Ser Ala		
att tgc ttt ttt cgc	tta aca atc	-25 tta gkt ttc Leu Xaa Phe		tgg 213 Trp

WO 99/53051 PCT/IB99/00712 359 -15 -10 . - 5 ggg tca act tca ttc tct twa gtt gck gca atg cta ttc cac tac cgg Gly Ser Thr Ser Phe Ser Xaa Val Ala Ala Met Leu Phe His Tyr Arg 10 gg 263 <210> 675 <211> 107 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 30..107 <221> sig\_peptide <222> 30..101 <223> Von Heijne matrix score 3.7000004768372 seq LLFLFFLFFFF/FF <400> 675 tgcactggca cacactcaca gctctgacc atg tca tca aac ata cag aga ctg 53 Met Ser Ser Asn Ile Gln Arg Leu -20 ggc ttc cct ctg ctt ttt ctt ttt ctt ttt ctt ttt ctt ttt ttt ttt 101 Gly Phe Pro Leu Leu Phe Leu Phe Leu Phe Leu Phe Phe Phe Phe -10 ttt ttt 107 Phe Phe <210> 676 <211> 276 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 70..276 <221> sig\_peptide <222> 70..270 <223> Von Heijne matrix score 3.70000004768372 seq LVLPLPMLPTSNR/KR <400> 676 gtcacagcac cctcctgaaa actgcagctt ccttctcacc ttgaagaata atcctagaaa 60 actcacaaa atg tgt gat gct ttt gta ggt acc tgg aaa ctt gtc tcc agt 111 Met Cys Asp Ala Phe Val Gly Thr Trp Lys Leu Val Ser Ser -65 gaa aac ttt gat gat tat atg aaa gaa gta gga gtg ggc ttt gcc acc 159 Glu Asn Phe Asp Asp Tyr Met Lys Glu Val Gly Val Gly Phe Ala Thr -50 -45 agg aaa gtg gct ggc atg gcc aaa cct aac atg atc atc agt gtg aat 207 Arg Lys Val Ala Gly Met Ala Lys Pro Asn Met Ile Ile Ser Val Asn -35 -30 -25 ggg gat gtg atc acc att ccc cac ctg gtc ctc ccc ctt ccc atg ctg 255 Gly Asp Val Ile Thr Ile Pro His Leu Val Leu Pro Leu Pro Met Leu

276

cca act tct aac cgc aag agg

Pro Thr Ser Asn Arg Lys Arg

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                                                                        120
agggttggac acgatggaaa tattttggtg aaccattcgt tcccttgggt ttctttctca
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tttggggagt gtggtttaca atgattggag caaaagtttc ctgaatcttt ttcttgtttc
                                                                       240
cattttattg catggtaaaa cacaatttat ccactttctt gtcaatgagt atctagttag
                                                                       300
attectgttt tttggetaat teaaataaaa etatga atg ttt ttg tae egg tet
                                                                       354
                                         Met Phe Leu Tyr Arg Ser
ttt ggt ggg cag ttg ctt tcc ttt ctc ttg ggt aca tac cta gga agg
                                                                       402
Phe Gly Gly Gln Leu Leu Ser Phe Leu Leu Gly Thr Tyr Leu Gly Arg
-15
                     -10
agg gaa gtt gct ggg cca cag cat ggc cag ttt tct aaa
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                                                                        60
gactggcttc gggagaaaca ccatccagaa gagacctttc aaaaaacttc tagagactcc
                                                                       120
ccaagacgta tgag atg ama ggc ttc ttc tgt ctg tgt gcg ttt aac tca
                                                                       170
                Met Xaa Gly Phe Phe Cys Leu Cys Ala Phe Asn Ser
                    -15
                                         -10
ttt ctc ctt agc ccc gag ggg
                                                                       191
Phe Leu Leu Ser Pro Glu Gly
<210> 679
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<213> Homo sapiens

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Val Thr His Pro Asn Ser Met Pro Ala Val Asn Ile Gln Tyr Glu Val

score 3.59999990463257 seq LHTSVTLFLLSYC/DC

<221> misc\_feature

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acccaatgaa agaagaaa atg aaa gcc ata aag aaa agt ctt aca gaa gaa Met Lys Ala Ile Lys Lys Ser Leu Thr Glu Glu -40	. 111
gaa tac ctg tac ctg gac ttt tct cac caa aca gaa gga tgc atc ttt	159
Glu Tyr Leu Tyr Leu Asp Phe Ser His Gln Thr Glu Gly Cys Ile Phe -30 -25 -20 -15	
cct ctt cat aca tct gta act tta ttt ctg tta tct tac tgt gac tgt Pro Leu His Thr Ser Val Thr Leu Phe Leu Leu Ser Tyr Cys Asp Cys -10 -5	207
aaa atc ttt aaa att tgc tta gtt gtc acc aaa gag gtg agt aga gat Lys Ile Phe Lys Ile Cys Leu Val Val Thr Lys Glu Val Ser Arg Asp	255
5 10 15 avn tca cta cta aga gat gac ctg atc cag gat gtt gaa ata cag att	303
Xaa Ser Leu Leu Arg Asp Asp Leu Ile Gln Asp Val Glu Ile Gln Ile 20 25 30	303
att tca agg Cag gag ctc cca cca a	328
Ile Ser Arg Gln Glu Leu Pro Pro 35 40	
<210> 683 <211> 447	
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<pre>&lt;221&gt; sig_peptide &lt;222&gt; 386427</pre>	
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ttaacatett ccactgaaaa gaaaagataa tgatataaat aaagcaattt aaatcaagte	60
taaggtatag gaaggtattt aagaaagaag caaacattct ctagatgttg ttatccaaaa tatattetet tttgcagttt actgaaataa tttetteagt gtgtgggaat tteetttgea	120 180
tecagettta etatagagat gacateacae caacagtgae acgaettgtt tacaagaggg	240
tggtataaac agcaaatgtt cttccttaaa acagatttct tgttgaactt caacagaaaa	300
agaagengta aatgtagaag gaagaacagg agatagtett taacatgtag ggtaaaatet aaggtagagg agagagcage tgata atg ttt tta tgt gtt tge tae ttt att	360 412
Met Phe Leu Cys Val Cys Tyr Phe Ile	
-10 agg aag tet act tee tte tte tee ata tet agt ag	447
Arg Lys Ser Thr Ser Phe Phe Ser Ile Ser Ser	
-5 1 5	
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                                                                         49
     Met Gly Lys Pro Arg Gly Gly Glu Met Leu Glu Val Val Lys Thr
                          -40
gtc tcc act ttc act ttg gga ggg tgg aaa ggg act gct cct gtg tcc
                                                                        97
Val Ser Thr Phe Thr Leu Gly Gly Trp Lys Gly Thr Ala Pro Val Ser
-30
                     -25
                                         -20
                                                              -15
tgc gcc tgg tgg ctg ctt ctc cca gtt tgg aag ctg gga ggg cag ctt
                                                                       145
Cys Ala Trp Trp Leu Leu Pro Val Trp Lys Leu Gly Gly Gln Leu .
                 -10
                                     - 5
gag cgc agg aag aat cca aag gaa tac tgt ctt ggc tcc tgg gtg tgg
                                                                       193
Glu Arg Arg Lys Asn Pro Lys Glu Tyr Cys Leu Gly Ser Trp Val Trp
                             10
ctc agt cct cag ctg gct cca agg
                                                                       217
Leu Ser Pro Gln Leu Ala Pro Arg
    20
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atogacattt toocta atg otg att tto acc ttt att tot act ttg otg ttt
                                                                       112
                  Met Leu Ile Phe Thr Phe Ile Ser Thr Leu Leu Phe
                      -15
gta ttc ttg gga gtt gtg gg
                                                                       132
Val Phe Leu Gly Val Val
<210> 686
<211> 260
<212> DNA
<213> Homo sapiens
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<221> CDS
<222> 120..260
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<222> 5..106 <221> sig\_peptide <222> 5..94 <223> Von Heijne matrix score 3.59999990463257 seq LCTFTLNLTAVRT/IX

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-55
 act aca aac caa acc aat gga tct tct act aca gga gat aaa cct gtt
                                                                       154
 Thr Thr Asn Gln Thr Asn Gly Ser Ser Thr Thr Gly Asp Lys Pro Val
                  -45
                                      -40
 gaa tca atg cag aca aaa ttg aac tac ctt aga aga aat cta ctc att
                                                                       202
 Glu Ser Met Gln Thr Lys Leu Asn Tyr Leu Arg Arg Asn Leu Leu Ile
                                  -25
                                                      -20
 tta gtt ggt att atc atc atg gtt ttt gtc ttt atc tgt ttt tgt tat
                                                                       250
 Leu Val Gly Ile Ile Ile Met Val Phe Val Phe Ile Cys Phe Cys Tyr
         -15
                              -10
ctc cat tat aat tgt ctg agc gat gat gcg tcc aaa gca gga atg gtc
                                                                       298
Leu His Tyr Asn Cys Leu Ser Asp Asp Ala Ser Lys Ala Gly Met Val
 aag aaa aaa ggc ata gca gcc aag tca tct aaa aca tca ttc agt gaa
                                                                       346
Lys Lys Gly Ile Ala Ala Lys Ser Ser Lys Thr Ser Phe Ser Glu
                 20
                                     25
gcc aag aca gcc tct caa tgc agt tca gaa aca caa acc ggg
                                                                       388
Ala Lys Thr Ala Ser Gln Cys Ser Ser Glu Thr Gln Thr Gly
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                                                                       120
acacaggaca ccaagtccct aggctgtaca cagcactggg accctgggcc ctgcccatgg
                                                                       180
aacaattttt tootootaaa tottoaggoo tgtgatggga ggggotacog caaaggtoto
                                                                       240
tgacatgece cagatacatt tteectattg tettggggat taacatttgg etectegtta
                                                                       300
ctt atg caa att tot goa goo ago ttg aat tto too toa aaa aat gga
                                                                       348
    Met Gln Ile Ser Ala Ala Ser Leu Asn Phe Ser Ser Lys Asn Gly
                -25
                                     -20
att ttc ttt tct tta aca ttg tca ggc tgc aaa ttt tcc aaa ctt tta
                                                                       396
Ile Phe Phe Ser Leu Thr Leu Ser Gly Cys Lys Phe Ser Lys Leu Leu
                                - 5
tgc cct ttt ggg
                                                                       408
Cys Pro Phe Gly
    5
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score 3.59999990463257 seq LVWDCLLPPPSFF/LL

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ggg gtc gcg ccg tgg cgg agc agc ctc cat ccc tgt gag atc act gcc	97
Gly Val Ala Pro Trp Arg Ser Ser Leu His Pro Cys Glu Ile Thr Ala -25 -20 -15	
ctg age caa tee cta cag eee tta egg aag etg eet ttt aga gee tet '	145
Leu Ser Gln Ser Leu Gln Pro Leu Arg Lys Leu Pro Phe Arg Ala Ser	
-10 -5 1 5 ygc acg gg	
Xaa Thr	153
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<2113 493 <212> DNA	
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·	118
gcg ccc aag ggc aaa gtg ggc acg aga ggg aag aag cag ata ttt gaa	166
Ala Pro Lys Gly Lys Val Gly Thr Arg Gly Lys Lys Gln Ile Phe Glu	
-45 -40 -35	
gag aac aga gag act ctg aag ttc tac ctg cgg atc ata ctg ggg gcc Glu Asn Arg Glu Thr Leu Lys Phe Tyr Leu Arg Ile Ile Leu Gly Ala	214
-30 -25 -20	
aat gcc att tac tgc ctt gtg acg ttg gtc ttc ttt tac tca tct gcc	262
Asn Ala Ile Tyr Cys Leu Val Thr Leu Val Phe Phe Tyr Ser Ser Ala -15 -5	
ten bit ton one ton the one of the one	
Ser Phe Trp Ala Trp Leu Ala Leu Gly Phe Ser Leu Ala Val Tyr Gly	310
1 5 10 15	
gee age tac cac tet atg age teg atg gea ega gea geg tte tet gag	358
Ala Ser Tyr His Ser Met Ser Ser Met Ala Arg Ala Ala Phe Ser Glu 20 25 30	
gat ggg gcc ctg atg gat ggt ggc atg gac ctc aac atg gag caq qqc 4	106
Asp Gly Ala Leu Met Asp Gly Gly Met Asp Leu Asn Met Glu Gln Gly	-
35 40 45	

371 Met Ala Glu His Leu Lys Asp Val Ile Leu Leu Thr Ala Ile Val Gln 55 gtg ctc agc tgc ttc tct ctc tat gtc tgg tcc ttc tgg 493 Val Leu Ser Cys Phe Ser Leu Tyr Val Trp Ser Phe Trp 70 <210> 698 <211> 174 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 8..172 <221> sig\_peptide <222> 8..94 <223> Von Heijne matrix score 3.59999990463257 seq AFNKAVWFTPCSC/QE <400> 698 aacaaag atg gcg gcg gtg act gtg acg gtg acg aag acg gcg gcg 49 Met Ala Ala Val Thr Val Thr Lys Thr Ala Ala Ala -25 -20 gcg acg gca ttt aac aag gcg gtg tgg ttt act cca tgc agt tgt cag 97 Ala Thr Ala Phe Asn Lys Ala Val Trp Phe Thr Pro Cys Ser Cys Gln -10 - 5 gag gta agt agc agg ctg ccg gct cgg acg gcg acg cgg cag gac 145 Glu Val Ser Ser Arg Leu Pro Ala Arg Thr Ala Ala Thr Arg Gln Asp agg gcg gat aag aag gag cgg ccc tgt gg 174 Arg Ala Asp Lys Lys Glu Arg Pro Cys <210> 699 <211> 300 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 199..300 <221> sig peptide <222> 199..255 <223> Von Heijne matrix score 3.59999990463257 seq PGSAICLWHSTLG/GX <221> misc\_feature <222> 261 <223> n=a, g, c or t <400> 699 attttgtctc ggcagcggtg gccgwagctc catcgcattt tatgtttctg gcgagaaggg 60 aacggagttt tcatcaggta gattggtttt trtgcggccg tcctccaccg tttcctccag 120 gacagcacct agtcgtggcc ggaggagtct catagctgtc agaaagaata agactgattt 180 tatgggaaaa ttaagcag atg ctc cag ttt gag aaa cct gga tct gcg atc 231 Met Leu Gln Phe Glu Lys Pro Gly Ser Ala Ile -15 tgt ttg tgg cac agc act ttg gga ggy ymn ggc ggg cgt gag att gds

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Су	5 Le	u Tı	гр Ні -5	is Se	er Tì	nr Le	eu G	ly GI	ly xa	a Gl	y Gl	y Ar	g Gl	u Il	e Xaa	.•
			ga co :g Pi				ly									_ 300
<2:	10> 11> 12> 1 13> 1	159 DNA	sap	oiens	. ·											1 .
	21> (	CDS 86	157													·
<22	2> { 3> \ 8	36 Jon scor	pept 139 Heij e 3. LAIL	ne m 5999	9990	4632					·					
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cta Leu	aaa Lys	tgg Tr	g gti va:	L ag L Se: -5	c aat	t tc n Se:	t aa r Ly	g ag s Se	t ttt r Phe	t ttg e Lev	gtg Val	aag Lys	gca Ala 5	tcg Ser	ı aa	159
<21 <21	0> 7 1> 2 2> D 3> H	74 NA	sapi	ens					,							·
	1> C	DS 62	.73						·		ı	• ,				1.
(22	2> 4: 3> V s	69 on H core	epti 0 eijn 3.5 QTLA	e ma	9904	6325	5 <b>7</b> -		•		•					
	)> 7	01					tggt	c tc	actg	agtt	cta	Me			tg ca eu Gl	
hr	ctc Leu -10	gca Ala	ttc Phe	tgg Trp	tca Ser	gcc Ala -5	tat	gtg Val	cca Pro	tgc Cys	cag Gln 1	acc Thr	caq	gac Asp	cgg Arg 5	105
at sp	ġcc Ala	ccg Pro	cgc Arg	ctc Leu 10	acc Thr	ctg Leu	gag Glu	cag Gln	att Ile 15	Asp	ctc	ata Ile	cgc Arg	cgc Arg 20	atq	153
gt	gcc Ala	tcc Ser	tat Tyr 25	tct Ser	gag Glu	ctg Leu	gag Glu	ctt Leu 30	gtg	acc	tcg Ser	gct Ala	aaa Lys 35	act	ctg Leu	201
ac sn	gac Asp	act Thr 40	cag Gln	aaa Lys	ttg Leu	gcc Ala	tgc Cys 45	ctc	atc Ile	ggt Gly	gta Val	gag Glu 50	aat	ggc Gly	cac His	249
cg	ctg	gac	aat		ctc	tcc		g								274

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373
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                                                                        60
atttgatttt tcaagtgagt tattaggata taggtgggag tggaga atg cct gcc
                                                                       115
                                                    Met Pro Ala
tgc ctt tct tcc ttt gtc att ccc tct ctc ctt tct ccc tcc tcc cct
                                                                       163
Cys Leu Ser Ser Phe Val Ile Pro Ser Leu Leu Ser Pro Ser Ser Pro
    -10
                         - 5
ccc tcc ata ggg
                                                                       175
Pro Ser Ile Gly
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                                                                        60
tcgcccactt gttgatgagg ttgtttttt cttgtaaatt tgtttgtgtt cattgtaagt
                                                                       120
tctggatatt agccctttgt cagatgagta gattgtaaaa attttctccc attctacagg
                                                                       180
ttgcctgttc actctg atg gta gtt tct ttt gct ggt tct tgc aca att cta
                                                                       232
                  Met Val Val Ser Phe Ala Gly Ser Cys Thr Ile Leu
                      -15
ggc gcc agt agc cat tca ttc ccc att gaa gtc agc ctg ttc cca gtg
                                                                       280
Gly Ala Ser Ser His Ser Phe Pro Ile Glu Val Ser Leu Phe Pro Val
                                                     10
gac tgt ggc ttc ctc ttg
                                                                       298
Asp Cys Gly Phe Leu Leu
        15
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Met Cys Cys Pro Gly

-20

tgg aac gca gtg tcg caa tct tgg ctc gct gca cct tcc acc tcc tgg
Trp Asn Ala Val Ser Gln Ser Trp Leu Ala Ala Pro Ser Thr Ser Trp

-15

-10

-5

gtt caa gag att ctc gta ctt cag cct cca ggg
Val Gln Glu Ile Leu Val Leu Gln Pro Pro Gly

<210> 705

<211> 433

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> 225..431

<221> sig\_peptide

<222> 225..386

<223> Von Heijne matrix score 3.5 seq IRCPLIFLXXVSG/TX

<400> 705

agaggactay gcgagagcgt ctacggttgt gccaaaggaa aaaaaatgtt cctaagaaaa 60 gagtatacaa agttgtgttc atcaaagtct ggaacccaaa ggtgtccctc caaagctgta 120 cacgacagag aaaacgcgaa ctgaaagaag aagcaggtcc caaggggcca ggcgcctcct 180 ccacctcctc ctcctcctag gattaacctc catttcagct aatc atg gga gag att 236 Met Gly Glu Ile aaa gtc tct cct gat tat aac tgg ttt aga ggt aca gtt ccc ctt aaa 284 Lys Val Ser Pro Asp Tyr Asn Trp Phe Arg Gly Thr Val Pro Leu Lys -45 -40 -35 aab dtw atk gtg gat gat gat gac agt aag ata tgg tcg chc tat gac 332 Xaa Xaa Xaa Val Asp Asp Asp Ser Lys Ile Trp Ser Xaa Tyr Asp -30 -25 -20 gcg ggc ccc cga agt atc agg tgt cct ctc ata ttc ctg cyc yct gtc 380 Ala Gly Pro Arg Ser Ile Arg Cys Pro Leu Ile Phe Leu Xaa Xaa Val -10 agt gga act gha gat gtc ttt ttc cgg cag att ttg gct ctg act gga 428 Ser Gly Thr Xaa Asp Val Phe Phe Arg Gln Ile Leu Ala Leu Thr Gly tgg gg 433 Trp

<210> 706

15

<211> 419

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10 aac gwg

382

<222> 284..418 <221> sig\_peptide <222> 284..331 <223> Von Heijne matrix score 3.5 seg SHSHLSLVGHSRA/CG <400> 706 attgaaaatc attaaaaatc ttagcaattg ttttaaatta tctaattttt ttctccaaat aatatctatt ttagcagcca aatcaccaca aatcattggt ttttatcttt agttgtgggt 120 gcacagcggg tgcgtgtatt ttggggcatg tgaggtgtct tgatgcgttc atgcagtgtg 180 taacagtcac atcagggtaa atgggacatc tttcacctca agcatttatc cttcgtgtta 240 tggacaccct cagctggaaa ggggggctgc gtcgtgagta tga atg gat gca agt 295 Met Asp Ala Ser cat age cae ctg age ctg gtg ggg cae age agg gcc tgt gga gtc aca 343 His Ser His Leu Ser Leu Val Gly His Ser Arg Ala Cys Gly Val Thr -10 -5 tee egg eet eat get egg eat agg gga ege tge tta ggt eea tge agt 391 Ser Arg Pro His Ala Arg His Arg Gly Arg Cys Leu Gly Pro Cys Ser 10 15 cgc tca ggg ccc agg ctg tgc agc gcc a 419 Arg Ser Gly Pro Arg Leu Cys Ser Ala 25 <210> 707 <211> 382 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 200..382 <221> sig\_peptide <222> 200..301 <223> Von Heijne matrix score 3.5 seq LISHDPWPRGAFA/LS <221> misc\_feature <222>. 365 <223> n=a, g, c or t <400> 707 gttacttatg gttgagagag aatatttttc agattttatt ggacattgat atttgtaaat 60 tgttcattcc ttttgcccag ttttctattg agtggttcat agtttctcat gggtatccaa 120 gagttctgga tatgtagagg tggagggtca atctcatcay ttccttgttt taaaaatctt 180 ccatggtttt gtcatcact atg ggc tca aac gcc gtg gtg tgg cat aca aag 232 Met Gly Ser Asn Ala Val Val Trp His Thr Lys -30 ccc tca ctt ctg aac cac cct gct tcc agc ctc atc tcc cat gat ccc 280 Pro Ser Leu Leu Asn His Pro Ala Ser Ser Leu Ile Ser His Asp Pro -15 tgg cca cgc ggt gcg ttt gcg ctt tca tgt cca agt gct tcc ttc atg 328 Trp Pro Arg Gly Ala Phe Ala Leu Ser Cys Pro Ser Ala Ser Phe Met -5 ttg ttt tct tcc tta caa tgc cct ttc cct tat tgd naa aca gag tgc 376 Leu Phe Ser Ser Leu Gln Cys Pro Phe Pro Tyr Xaa Xaa Thr Glu Cys

Asn Xaa		•	
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<400> 708  aagtgacgct acaggggcca gctatgctc gctgacagcg ttcaagttgg aatcctgga aggccacgct gtccgtccgc agtaccgac cctacgagac aagaagggct tcatcatca	g gggaggtgtt g cctgcagcag a gcag atg a Met L	tttcctgtcg tacg gagcattggt ttga ag gag gat ggc go ys Glu Asp Gly A -15	tgggac 120 aaaggc 180 cc tgt 235 la Cys
ctc ttc cgg gct gta gct gac cag Leu Phe Arg Ala Val Ala Asp Gln -10 -5	Val Tyr Gly	Asp Gln Asp Met	His 5
gag gtt gtg cga aag cat trc atg Glu Val Val Arg Lys His Xaa Met 10	Asp Tyr Leu 15	Met Lys Asn Ala	Asp
tay ttc tcc arc tat gtc aca gag Tyr Phe Ser Xaa Tyr Val Thr Glu 25	gac ttt acc Asp Phe Thr 30	acc tac att akc Thr Tyr Ile Xaa 35	agg 379 Arg
aag cg Lys			384
<210> 709 <211> 149 <212> DNA <213> Homo sapiens			
<220> <221> CDS <222> 76147			
s221> sig_peptide s222> 76138 s223> Von Heijne matrix score 3.5 seq VLIMIXEAXNVWC/GD			
221> misc_feature 222> 123124 223> n=a, g, c or t			·
400> 709 cctaatatt aaaaatcttc ttctctaaaa gctcagttt gatat atg gtt cac ctc Met Val His Leu -20	att ctt act Ile Leu Thr	accctgatca agagg gaa gtc ctc att Glu Val Leu Ile	atg 111 Met
tc akc gag gcn nsg aat gtg tgg			-10 149

-5

٦ <210> 710 <211> 167 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 15..167 <221> sig\_peptide <222> 15..155 <223> Von Heijne matrix score 3.5 seq CLXFGILASEVYS/WN <400> 710 atatttcatg gcga atg tac cac aat tta ttt gct ctg ttg ata gac 50 Met Tyr His Asn Leu Phe Ala Leu Leu Leu Ile Asp , -45 -40 att cat gtt gtt cta gtt ttt tac tgc ctg gat ctc tta atg att cat 98 Ile His Val Val Leu Val Phe Tyr Cys Leu Asp Leu Leu Met Ile His -30 -25 att ttc tat tgt aaa tac tgc ctt gka ttt ggk att tta gca agt gaa 146 Ile Phe Tyr Cys Lys Tyr Cys Leu Xaa Phe Gly Ile Leu Ala Ser Glu -15 -10 gtc tat tct tgg aac att tac 167 Val Tyr Ser Trp Asn Ile Tyr <210> 711 <211> 215 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 84..215 <221> sig\_peptide <222> 84..170 <223> Von Heijne matrix score 3.5 seg SPLCSXSSGYCXA/FP <400> 711 ccgcttttgg ctgcatcagc cggggattgc cggcgccagg tgctgggggc gactcggaca 60 gcgggagcgt ggggtggagt agg atg gag tot occ too cga got ggg ggt gtr 113 Met Glu Ser Pro Ser Arg Ala Gly Gly Val -25 . gro ctm vga aag got got tog cog ctg tgt tog gmv ago tot gga tac 161 Xaa Leu Xaa Lys Ala Ala Ser Pro Leu Cys Ser Xaa Ser Ser Gly Tyr -15 -10 tgc rgg gct ttt ccg cgg agg agc gcc cgc cgg cat ctg cat ccg gga 209 Cys Xaa Ala Phe Pro Arg Arg Ser Ala Arg Arg His Leu His Pro Gly 10 cac ggg 215 His Gly 15

<210> 712

<211> 241

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actatecttt ceteattgaa tigetgigat acettigitg caaatcaget gietgeag
                                                                        58
atg tgg agg tat gtt tct aga ctt tct tct gtt cca ttg atc agc ttg
                                                                       106
Met Trp Arg Tyr Val Ser Arg Leu Ser Ser Val Pro Leu Ile Ser Leu
                     -20
                                         -15
tot gto ttg atg cca gta cag cac tcc cct gat ttt tgt agc ttt att
                                                                       154
Ser Val Leu Met Pro Val Gln His Ser Pro Asp Phe Cys Ser Phe Ile ,
                · - 5
gta agt aca gtt atc cct tgg ttt cct tgg gga att ggt tcc agg acc
                                                                       202
Val Ser Thr Val Ile Pro Trp Phe Pro Trp Gly Ile Gly Ser Arg Thr
        10
                             15
ctc atg gat ata aaa atc ctg gga tgc tcg agt cca ggg
                                                                       241
Leu Met Asp Ile Lys Ile Leu Gly Cys Ser Ser Pro Gly
    25
<210> 713
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<221> sig peptide
<222> 276..365
<223> Von Heijne matrix
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      seq NLLKLSSHSPTCA/CK
<221> misc_feature
<222> 154,217
<223> n=a, g, c or t
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tatgtacatt tgtcaaaact cagaaaatgt atatataata tgtgtgcata tgattttaag
                                                                       60
tagttttaca taaaaagata agcaaatatt ggatgctggt taacactaag catgctgaaa
                                                                      120
tatttagagg gaagagtatt attgtctaca atyngcttta aagacaccaa aaataaggtg
                                                                      180
grttaattwa wkggsywwgg grmdwtggat aaatggnkag awatgtgata aagcaagtct
                                                                      240
aatagaattt tgtggcagaa tctaatggcg gctat atg gat gtt agc tgt aaa
                                                                      293
                                       Met Asp Val Ser Cys Lys
                                       -30
att ctt tac aat gtg att gaa aaa ttt tgc aat aat ctg ttg aag ctt
                                                                      341
Ile Leu Tyr Asn Val Ile Glu Lys Phe Cys Asn Asn Leu Leu Lys Leu
                -20
                                    -15
tct tcc cat tcc cct act tgt gct tgc aaa cta aa
                                                                      376
Ser Ser His Ser Pro Thr Cys Ala Cys Lys Leu
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                                                                      60
 tattcagttt ttgcccagag ttattatatc tggggaataa acagaggaca cacacccaga
                                                                     120
 ggctgccagt agcaaaaatc actgtaattc aaaaagcatg acactacggt agtgaaatta
                                                                     180
 teacactttt etttgeatag ageagtttae ttgtg atg att tte aaa gat gtg
                                                                     233
                                       Met Ile Phe Lys Asp Val
                                       -20
 ttc tcc cac ttg tca ggt tca tct ctt caa ctg tgt gtc gca caa ttt
                                                                     281
 Phe Ser His Leu Ser Gly Ser Ser Leu Gln Leu Cys Val Ala Gln Phe
                 -10
 ctc gaw ctc agt gct gtt gac at
                                                                     304
 Leu Xaa Leu Ser Ala Val Asp
 <210> 715
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                                                                      60
 aatactatag gtttttgctt tgtggttaac atg aag ctt aca aaa aat atc tta
                                                                     114
                                 Met Lys Leu Thr Lys Asn Ile Leu
                                                 -40
twa gta ata ata ggc tgt ttt aag ctg ata gcc tac aaa aac tct gta
                                                                     162
 Xaa Val Ile Ile Gly Cys Phe Lys Leu Ile Ala Tyr Lys Asn Ser Val
                        -30
                                            -25
 ctg tac ttt tac tct aac ttc tca ttt tct ttt ctt ttc ttt ttc
                                                                     210
 Leu Tyr Phe Tyr Ser Asn Phe Ser Phe Ser Phe Leu Phe Phe Phe
                    -15
                                        -10
 242
 Leu Ser Phe Phe Phe Phe Phe Phe Phe
 <210> 716
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                                                                        60
 ctggctcttt cctcttcgcc ttaaattcgg gtgtctttt atg aat aat caa aag
                                                                       114
                                            Met Asn Asn Gln Lys
 cag caw rag cca acg cta tca ggc cag cgt ttt aaa act aga aaa aga
                                                                       1.62
 Gln Xaa Xaa Pro Thr Leu Ser Gly Gln Arg Phe Lys Thr Arg Lys Arg
                             -75
                                                  -70
 gat gaa aaa gag agg ttt gac cct act cag ttt caa gac tgt att att
                                                                       210
 Asp Glu Lys Glu Arg Phe Asp Pro Thr Gln Phe Gln Asp Cys Ile Ile
                         -60
                                             -55
 caa ggc tta act gaa acc ggt act gat ttg gaa gca gta gct aag ttt
                                                                       258
Gln Gly Leu Thr Glu Thr Gly Thr Asp Leu Glu Ala Val Ala Lys Phe
 -50
                     -45
                                         -40
 ctt gat gct tct gga gca aaa ctt gat tac cgt cga tat gca gaa aca
                                                                       306
Leu Asp Ala Ser Gly Ala Lys Leu Asp Tyr Arg Arg Tyr Ala Glu Thr
                 -30
                                     -25
ctc ttt gac att ctg gtg gct ggt kga atg ctg gcc cca ggt ggt aca
                                                                       354
Leu Phe Asp Ile Leu Val Ala Gly Xaa Met Leu Ala Pro Gly Gly Thr
            -15
                                 -10
ctg gca gat gac atg atg cvq
                                                                       375
Leu Ala Asp Asp Met Met Xaa
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tatcctttca ttctcttagg ttcatttggt ctgatggatt caggtaccat tgaaattctg
                                                                       120
atagtttcaa aatcttttat ctccaggttt gatctctctt gtgaactctg gaactgtatt
                                                                       180
cccaattgtc aattggacat ccctacgtat gggacctcag atatttcaaa catgatgtgt
                                                                       240
ccaaqtctgt atcacttctg gccatcatat tgttctttta tttttccaaa tttcacatca
                                                                       300
ccagtaacaa actagctgtg atc atg gca gat agc ctg gaa ata aaa ctc ccc
                                                                       353
                          Met Ala Asp Ser Leu Glu Ile Lys Leu Pro
                                   -15
ttt tta ccc ttt gca cag caa att gac atc aaa tcc tgt ttc tac ttt
                                                                       401
Phe Leu Pro Phe Ala Gln Gln Ile Asp Ile Lys Ser Cys Phe Tyr Phe
ttt ttt ttw aac wat kgc ttc cct agg g
                                                                       429
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Phe Phe Xaa Asn Xaa Xaa Phe Pro Arg
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<221> misc_feature
<222> 155
<223> n=a, g, c or t
<400> 718
tga atg gac aga aaa tgg acc tgg aag aga ggg caa agg tca cat ctg
                                                                        48
    Met Asp Arg Lys Trp Thr Trp Lys Arg Gly Gln Arg Ser His Leu
    -35
                         -30
gag tea gge cag get gee eeg gee aet gea gea get aeg gea gea tet
                                                                        96
Glu Ser Gly Gln Ala Ala Pro Ala Thr Ala Ala Ala Thr Ala Ala Ser
                    -15
                                         -10
gcc aca acg ggg gca agt gtg tgg aga agc aca atg ggc wac ctg tgt
                                                                       144
Ala Thr Thr Gly Ala Ser Val Trp Arg Ser Thr Met Gly Xaa Leu Cys
gat tgc acc and dca cct tat gaa ggg ccc ttt tgc aaa aaa gag gtt
                                                                       192
Asp Cys Thr Xaa Xaa Pro Tyr Glu Gly Pro Phe Cys Lys Lys Glu Val
tet get gtt ttt gag get gge acg teg gtt act tac atg ttt caa gaa
                                                                       240
Ser Ala Val Phe Glu Ala Gly Thr Ser Val Thr Tyr Met Phe Gln Glu
ccc tat cct gtg acc aag aat ata agc ctc tca tcc tca gct att tac
                                                                       288
Pro Tyr Pro Val Thr Lys Asn Ile Ser Leu Ser Ser Ser Ala Ile Tyr
                    50
aca gat toa got coa too aag gaa aac att goa ott ago ttt gtg aca
                                                                       336
Thr Asp Ser Ala Pro Ser Lys Glu Asn Ile Ala Leu Ser Phe Val Thr
                                    70
acc caa gca ccg gg
                                                                       350
Thr Gln Ala Pro
            80
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     seg VLSIKHLPPQLRA/FQ
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ccctgtgagc ctgtaggagt aga atg gct ccc caa atg tat gag ttc cat ctg	113
Met Ala Pro Gln Met Tyr Glu Phe His Leu	
-40 -35 i	
cca tta tcc cca gag gag ttg ttg aaa agt gga ggg gtg aat cag tat	161
Pro Leu Ser Pro Glu Glu Leu Leu Lys Ser Gly Gly Val Asn Gln Tyr	
-30 -25 -20	
gtt gtg caa gag gta ctg tcc atc aaa cat ctt cca cca cag ctt aga	209
Val Val Gln Glu Val Leu Ser Ile Lys His Leu Pro Pro Gln Leu Arg	
-15 -10 -5	
gct ttt cag gct gcc ttt cga gct cag ggg ccc ctg gct atg ctg cag	257
Ala Phe Gln Ala Ala Phe Arg Ala Gln Gly Pro Leu Ala Met Leu Gln	
1 5 10 15	
cac ttt gat act atc tac agc att ttg cat cac ttt cga agt ata gat	3.05
His Phe Asp Thr Ile Tyr Ser Ile Leu His His Phe Arg Ser Ile Asp	. 3.03
20 25 30	
30	
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C2137 Hollio Suprem	
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score 3.5	
seq AVQVVGSWPSVQP/RE	
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Met Ala Ala Val Gln Val Val Gly Ser Trp Pro Ser Val Gln Pro	
-15 -10 -5	
cgg gag gca ccg cgg gaa gca atc cct gag cga ggc aat ggg ttt cgc	98
Arg Glu Ala Pro Arg Glu Ala Ile Pro Glu Arg Gly Asn Gly Phe Arg	
1 5 10 15	
ctc ttg tct gcc agg ctc tgc gcc ctg cgc ccg gat gac agc agc tcc	146
Leu Leu Ser Ala Arg Leu Cys Ala Leu Arg Pro Asp Asp Ser Ser Ser	140
20 25 30	
gcc cgm acc gag atc cac ctg mtc ttc gat cag ctc atc tcc gag aac	104
Ala Arg Thr Glu Ile His Leu Xaa Phe Asp Gln Leu Ile Ser Glu Asn	194
· 3F	
35	
tac age gag ggc agt ggc gtg gcc ccg gag gac gtw agt gct ctt ctt	242
Tyr Ser Glu Gly Ser Gly Val Ala Pro Glu Asp Val Ser Ala Leu Leu	
50 55 60	
gtc cag gct tgc ggg	257
Val Gln Ala Cys Gly	
65	
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<211> 360	
<212> DNA	
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· •	
<220>	
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<222> 217360	

<222> 63..473

383 .

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 <222> 217..306
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       seq FLFFLQFSFPLYY/LF
 <221> misc_feature
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cattratett tttteettta ttttetgttg etttgtettt ttgtaatgee teetggggea
                                                                       120
atttetttga titttatett geagttette tattgagttt tgeatgttgg etateatgtt
                                                                       180
ttaaattttc attttcata gtattctgtc ctatgg atg ttt cat ggc tgt cat
                                                                       234
                                         Met Phe His Gly Cys His
                                         -30
att tta tct ttt ctg agg ata tca act aga ggt ttt ctt ttt ttt ctt
                                                                       282
Ile Leu Ser Phe Leu Arg Ile Ser Thr Arg Gly Phe Leu Phe Phe Leu
                 -20
                                     -15
caa tit too tit cot cig tat tat cic tit cgg ngg nit tic cot cag
                                                                       330
Gln Phe Ser Phe Pro Leu Tyr Tyr Leu Phe Arg Xaa Xaa Phe Pro Gln
tct ttc atg ttg gag gca ttt gtc aga tgt
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Ser Phe Met Leu Glu Ala Phe Val Arg Cys
    10
                         15
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                                                                        60
gtt atg tat aga cat tcc aaa cag cgt aat aat gtc cca tgc ctt gta
                                                                       108
    Met Tyr Arg His Ser Lys Gln Arg Asn Asn Val Pro Cys Leu Val
        -25
                            . ~20
                                                 -15
ctc tac gcc cct tgg gtc cct ccc ctc ctc cta gct ttc tgg ggc tgg
                                                                       156
Leu Tyr Ala Pro Trp Val Pro Pro Leu Leu Leu Ala Phe Trp Gly Trp
    -10
                        -5
tgg ctc ctg gag cag ggt ctt ttt ttt ttt ttt tt
                                                                       191
Trp Leu Leu Glu Gln Gly Leu Phe Phe Phe
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385 -

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tetttttttg geetaettag atetgtttte etttettgee ttaaatggga attgetagag
                                                                       120
gmat atg ttt cta act ttt ttt ttc tgc aca caa gtt cat ggt cct tct
                                                                       169
     Met Phe Leu Thr Phe Phe Cys Thr Gln Val His Gly Pro Ser
                                      -5
ata ctt gat agc cca gct
                                                                       187
Ile Leu Asp Ser Pro Ala
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                                                                        56
                                           Met Val Thr Leu Trp Ile
ttt caa ttt ttc ttg tgt ttg act tgt aaa gct tat aat tta aga aac
                                                                       104
Phe Gln Phe Phe Leu Cys Leu Thr Cys Lys Ala Tyr Asn Leu Arg Asn
tgt aat gat ggg aag ggh wga gsm tca gwg gtg ctt gga ttg gaa caa
                                                                       152
Cys Asn Asp Gly Lys Gly Xaa Xaa Ser Xaa Val Leu Gly Leu Glu Gln
                        15
mnr cta cct gaa tct gct ggt atg gta caw ttt tta ggt ttg aaa cac
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Xaa Leu Pro Glu Ser Ala Gly Met Val Xaa Phe Leu Gly Leu Lys His
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agg tgg g
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Arg Trp
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ctt ggt gcc ctg cat ccc Leu Gly Ala Leu His Pro	c aga tgc tct a	gt caa ggc ttg agg er Gln Gly Leu Arg	ctt gcr 152 Leu Ala
sct tct gaa gcc Xaa Ser Glu Ala 20			164
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agc ttc gac ttc gtg gct Ser Phe Asp Phe Val Ala -30 -25	Leu Asn Leu Th	eg gge tte gtg gee	tac agt 219 Tyr Ser -15
gta ttc aac atc ggc ctc Val Phe Asn Ile Gly Leu -10		ro Xaa Xaa Xaa Gly	gca gtt 267
tct cct caa ata ccc caa Ser Pro Gln Ile Pro Gln 5			
ctt ctt Leu Leu 20			321
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								Glu	Pro	Leu	Ala	Ala	Tyr	Pro	Leu		
							1				5						
aaa	tgt	tcc	999	CCC	aga	gca	aag	gta	ttt	gca	gtt	ttg	ctg	tct	ata	9	99
	Cys	Ser	Gly	Pro		Ala	Lys	Val	Phe		Val	Leu	Leu	Ser	Ile		
10					15					20					25		
															aaa	. 14	17
Val	Leu	Cys	Thr		Thr	Leu	Phe	Leu		Gln	Leu	Lys	Xaa	Leu	Lys		
	·			30					35				•	40			
cct	aaa	atc	aac	agc	ttt	tat	gcc	ttt	gaa	gtg	aag	gat	gca	aaa	gga	19	95
Pro	Lys	He		Ser	Pne	Tyr	Ala		GIu	Val	Lys	Asp		Lys	Gly		
			45					50					55				
aga	act	gtt	tct	ctg	gaa	aag	tat	aaa	ggc	aaa	gtt	tca	cta	gtt	gta	24	13
Arg	Thr		Ser	Leu	Glu	Lys		Lys	Gly	Lys	Val		Leu	Val	Val		
		60					65					70			,		
aac	gtg	gcc	agt	gac	tgc	caa	ctc	aca	gac	aga	aat	tac	tta	999	ctg	29	)1
Asn		Ala	Ser	Asp	Cys		Leu	Thr	Asp	Arg		Tyr	Leu	Gly	Leu		
	75					80					85			•			
aag	gaa	ctg	cac	aaa	gag	ttt	gga	cca	tcc	cac	ttc	agc	gtg	ttg	gct	33	19
	GIu	Leu	HIS	гàг		Pne	Gly	Pro	Ser			Ser	Val	Leu	Ala		
90					95					100					105		
ttt	ccc	tgc	aat	cag	ttt	gga	gaa	tcg	gag	ccc	cgc	cca	agc	aag	gaa	38	17
Pne	Pro	Cys	Asn		Pne	GIY	GIu	Ser		Pro	Arg	Pro	Ser	_	Glu		
				110					115					120			
gta	gaa	tct	בבנ	gca	aga	aaa -	aac	tac	gga	gta	act	ttc	CCC	atc	ttc	. 43	5
vaı	GIU	ser		ATA	Arg	гÀг	Asn		GIA	vaı	Thr	Pne			Phe		
			125					130				-	135				
											ctg	С				47	2
HIS	ьys		ьys	116	Leu	GIY		GIU	Gly	GIU	Leu						
		140					145										
-216	1. 21					•											
	)> 73 l> 46																
	2 > D1																
		omo s	anie	ene.												•	
<b>CZ1</b> 3	)	טוווט ב	опрт	-115													
<220	١.	•															
	l> CI	16															
		)46	5														
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-400	)> 73																
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gccg	guu														ro Ser		. 1
		1	. C AL	,,, G	.u Al	.a nc	. L A.	La II	ii A	sp so	3 (		rg A	ry P	ro ser		
-a+	tat		aat	<b>a</b> a 3	art	_	att					-					
														gag	Gln	15	. 9
_	Cys	1111	GIY	GIY		vaı	vaı	Arg	PIO		Ala	vaı	Thr	GIU			
15					20					25					30		_
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ser	Tyr	met	GIU		vaı	vaı	Thr	Pne		GIN	Asp	vaı	Val	Pro	GIn		
				35					40					45			
_		_						_	_	_				gtc		25	5
Ala	Tyr			Thr	Pro	Leu	Thr		Glu	Lys	Glu	ГÀг		Val	$\mathtt{Trp}$	•	
			50					55					60				
														ctg		30	3
Val	Arg		GIU	Asn	Ala	Asp		Asn	Asp	Thr	Ser		Asn	Leu	Glu		
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ttt	cat	gaa	ata	cat	agt	act	999	agt	gaa	ccg	cct	ttg	ttg	att	aţg	35	1

388	
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Ile Gly Tyr Ser Asp Gly Met Gln Val Trp Ser Ile Pro Ile Xaa Gly	399
95 100 105 110 1	•
gaa sac aag agc tot tot otg tto gac atg goo caa tto gag ogg eta	447
Glu Xaa Lys Ser Ser Ser Leu Phe Asp Met Ala Gln Phe Glu Arg Leu	44/
115 120 125	
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ggagaagatg aaggaagcca aggatgcccg ctataccaat gggcacctct tcaccaccat ttcagtttca ggcatgacca tgtgct atg cct gta aca aga gca tca cag cca	180
Met Pro Val Thr Arg Ala Ser Gln Pro	233
1 5	
agg aag ccc tca tct gcc caa caa cag aaa gcg gcc ctg ctg aak aac	281
Arg Lys Pro Ser Ser Ala Gln Gln Gln Lys Ala Ala Leu Leu Xaa Asn	201
15 20 25	
aac acc gcc ttg cag tcc gtt tct ctt cga agt aag aca acc atc cgg	329
Asn Thr Ala Leu Gln Ser Val Ser Leu Arg Ser Lys Thr Thr Ile Arg	
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Glu Arg Pro Ser Ser	345
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gaagtgtata agatcagctt tatctttcca aatggagaca agtatgatgg tgactgtaca	120 180
agaacatett etggaateta egagagaaat qqaataqqta tteataceae teetaatogg	240
attgtctaca caggaagctg gaaagatgac aag atg aat ggt ttt gga aga ctt	294
Met Asn Gly Phe Gly Arg Leu	
1 5	
gag cat ttt tca gga gca gta tat gaa gga caa ttt aag gat aat atg	342
Glu His Phe Ser Gly Ala Val Tyr Glu Gly Gln Phe Lys Asp Asn Met	
10 15 20	
ttt cat gga ctg ggg act tac aca ttc cca aat ggg gca aag tat act	390
Phe His Gly Leu Gly Thr Tyr Thr Phe Pro Asn Gly Ala Lys Tyr Thr 25 30 35	
25 30 35 gga att tc	
Gly Ile	398

313

389 40 ·<210> 733 <211> 443 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 49..441 <400> 733 ggaagttett gggagegeea gtteegtetg tgtgttegag tggacaaa atg geg aag 57 Met Ala Lys atc gcc aag act cac gaa gat att gaa gca cag att cga gaa att caa 105 Ile Ala Lys Thr His Glu Asp Ile Glu Ala Gln Ile Arg Glu Ile Gln 10 ggc aag aag gca gct ctt gat gaa gct caa gga gtg ggc ctc gat tct 153 Gly Lys Lys Ala Ala Leu Asp Glu Ala Gln Gly Val Gly Leu Asp Ser 20 25 30 aca ggt tat tat gac cag gaa att tat ggt gga agt gac agc aga ttt 201 Thr Gly Tyr Tyr Asp Gln Glu Ile Tyr Gly Gly Ser Asp Ser Arg Phe 45 gct gga tac gtg aca tca att gct gca act gaa ctt gaa gat gat gac 249 Ala Gly Tyr Val Thr Ser Ile Ala Ala Thr Glu Leu Glu Asp Asp 60 gat gac tat tca tca tct acg agt ttg ctt ggt cag aag aag cca gga 297 Asp Asp Tyr Ser Ser Ser Thr Ser Leu Leu Gly Gln Lys Lys Pro Gly tat cat gcc cct gtg gca ttg ctt aat gat ata cca cag tca aca gaa 345 Tyr His Ala Pro Val Ala Leu Leu Asn Asp Ile Pro Gln Ser Thr Glu 85 90 cag tat gat cca ttt gct gag cac aga cct cca aag att gca gac cgg 393 Gln Tyr Asp Pro Phe Ala Glu His Arg Pro Pro Lys Ile Ala Asp Arg 105 110 gaa gat gaa tac aaa aag cat agg cgg acc atg ata att tcc cag agc 441 Glu Asp Glu Tyr Lys Lys His Arg Arg Thr Met Ile Ile Ser Gln Ser 120 125 gt 443 <210> 734 <211> 373 <212> DNA . <213> Homo sapiens <220> <221> CDS <222> 128..373 <400> 734 gagaagccgc agtctcgaga gcgtcaacga ggtgtttcgg tagtctctgg ccatcctttc 60 tgcgcacccg gtgtcgctgg gctgcacccc gggcggggac gtccgccggg cacgggaggg 120 ggccaag atg ccg atc aat aaa tca gag aag cca gaa agc tgc gat aat 169 Met Pro Ile Asn Lys Ser Glu Lys Pro Glu Ser Cys Asp Asn gtg aag gtt gtt gtt agg tgc cgg ccc ctc aat gag aga gag aaa tca 217 Val Lys Val Val Val Arg Cys Arg Pro Leu Asn Glu Arg Glu Lys Ser atg tgc tac aaa cag gct gtc agt gtg gat gag atg agg gga act atc 265

Met Cys Tyr Lys Gln Ala Val Ser Val Asp Glu Met Arg Gly Thr Ile

act gta cat aag act gat tot too aat gaa oot ooa aag aca ttt act

40

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Thr Val His Lys Thr Asp Ser Ser Asn Glu Pro Pro Lys Thr Phe Thr
                                  55
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                                                                        361
 Phe Asp Thr Val Phe Gly Pro Glu Ser Lys Gln Leu Asp Val Tyr Asn
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                             70
                                                  75
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                                                                        373
 Leu Thr Ala Arg
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                                                                       120
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                                                                       180
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                                                                       231
                         Met Pro Asn Arg Gly Gly Asn Gly Leu Ala
cct ggg gag gac aga ttc aaa cct gtg gta cca tgg cct cat gtt gaa
                                                                       279
Pro Gly Glu Asp Arg Phe Lys Pro Val Val Pro Trp Pro His Val Glu
gga gta gaa gtg gac tta gag tct att aga aga ata aac aag g
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Gly Val Glu Val Asp Leu Glu Ser Ile Arg Arg Ile Asn Lys
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                                                                       110
                Met Ser Leu Trp Leu Cys Phe Gln Cys Pro Leu Gly
gtt tcc aag agc aac aag aaa cga ata aat ctc tgt aat ggt ttc tgg
                                                                       158
Val Ser Lys Ser Asn Lys Lys Arg Ile Asn Leu Cys Asn Gly Phe Trp
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aat gaa aaa ata aaa aac agg ag
                                                                       181
Asn Glu Lys Ile Lys Asn Arg
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tgt agc agt cta ctc acg gcc cct gta ctt tgc tac tgg agg gcc tgt Cys Ser Ser Leu Leu Thr Ala Pro Val Leu Cys Tyr Trp Arg Ala Cys 30 35 40	146
cct ctg caa acc ca Pro Leu Gln Thr	160
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gta tta tta aac aca tgc tta tat gta cct tat ggg tat ttg tca ctt Val Leu Leu Asn Thr Cys Leu Tyr Val Pro Tyr Gly Tyr Leu Ser Leu 20 25 30	158
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tta atg acc aca aca agc aag cat gca gct tac tgc ttg aaa ggg tct	468
Met Thr Thr Ser Lys His Ala Ala Tyr Cys Leu Lys Gly Ser 1 5 10 15	
tgc ctc amc caa gct aga gtg cag tgg cct ttg aag cwt act aca gcc Cys Leu Xaa Gln Ala Arg Val Gln Trp Pro Leu Lys Xaa Thr Thr Ala	516
tea aac ttc tgg get caa gtg atc etc agc etc eca gtg gte ttt gta	564
Ser Asn Phe Trp Ala Gln Val Ile Leu Ser Leu Pro Val Val Phe Val 35 40 45	

392		
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ttt gaa gtc aac agt ttg cag aaa agc aac tgg Phe Glu Val Asn Ser Leu Gln Lys Ser Asn Trp 30 35	g ggg ttc tta ctt act p Gly Phe Leu Leu Thr 40	148
ggg ctt gtg ggt ggc acc ctg gtg gct gtg tac Gly Leu Val Gly Gly Thr Leu Val Ala Val Tyr 45	c gct gta gcc acg ccg r Ala Val Ala Thr Pro 55	196
ttt gta acg cca gcc ctt cga aaa gtc tgt ttg Phe Val Thr Pro Ala Leu Arg Lys Val Cys Leu 60 65	g cca ttt gta cct gca u Pro Phe Val Pro Ala 70	244
act atg aag cag att gaa aat gtt gtg aaa atg Thr Met Lys Gln Ile Glu Asn Val Val Lys Met 75	Leu Arg Cys Arg Arg 85	292
gga tcc ctt gtg gac atc ggt agt ggg gac gga Gly Ser Leu Val Asp Ile Gly Ser Gly Asp Gly 90 95 100	/ Arg Ile Val Ile Ala 105	340
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tgg aga aga caa cct gaa gct gtt cam ctt ctt Trp Arg Arg Gln Pro Glu Ala Val Xaa Leu Leu 30 35	gat aag att ttg aag Asp Lys Ile Leu Lys 40	146
aaa cac aaa cct gac ttc atc tca ttg ttc aaa Lys His Lys Pro Asp Phe Ile Ser Leu Phe Lys 45 50 55		194
gtt caa cag cat gag aag gtt cag aaa gcc agt Val Gln Gln His Glu Lys Val Gln Lys Ala Ser	aca gag gga gtc gcc	242

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Il	e Glr	Gly	gln G	Gln	Gly	Thr	Arg	Leu	Leu	Pro	Glu	Gln	Leu	Ile	Lys		
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Ğl	u Āla	Phe	lle	Leu	Ser	Asp	Leu	Phe	Āsp	Ile	Glv	Ğlu	Leu	Ala	Ala		,
		95			•	•	100				1	105			,		
at	t gag		ctt	ctt	act	gga			caa	cad	cca			cct	000		386
Va	l Glu	Len	Leu	Len	Ala	Glv	Glu	Hic	Gla	Gln	Ď*O	Uic	Dho	Dro	231		300
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7.0	t acc	aya Ama	Clu	Lua	yıa	אות ב	911	T and	ccg	tac	tgg	gat	gga	aag	cga		434
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12					130					135					14.0		
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aag tra tra act gcc aac caa g	aa aac aaa aat	5 Taa daa not off o	

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Lys Ile Ser Lys Thr Tyr Ser Ser Cys Leu Thr Glu Xaa Leu Tyr Pro	•
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Ser Ile Gln Ile Phe Ile Val Ser Ile Trp Ser Phe Phe Leu Phe Tyr
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ccgccacga atg ggg agg tgg gcc ctc gat gtg gcc ttt ttg tgg aag g	ca 351
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Gln Met Leu Lys Glu Gly Ala Lys His Phe Ser Gly Leu Glu Glu Ala 15 20 25	
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Val Tyr Arg Asn Ile Gln Ala Cys Lys Glu Leu Ala Gln Thr Thr Arg 30 35 40	
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Thr Ala Tyr Gly Pro Asn Gly Met Asn Lys Met Val Ile Asn His Leu 45 50 60	
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Glu Lys Leu Phe Val Thr Asn Asp Ala Ala Thr Ile Leu Arg Glu Leu 65 70 75	
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Glu Val Gln His Pro Ala Ala Lys Met Ile Val Met Ala Ser His Met 80 85 90	<b>331</b>
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Gly Ala Lys Asp Glu Cys Asn Val Val Glu Val Val Ala Arg Asn His
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Asp His Gln Glu Ile Ala Val Pro Val Ala Xaa Leu Lys Leu Ser Cys
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                                                                      101
Lys Arg Asp Leu Leu Phe Gln Ala Leu Gly Arg Thr Tyr Thr Asp Glu
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Glu Phe Asp Glu Leu Cys Phe Glu Phe Gly Leu Glu Leu Asp Glu Ile
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Thr Ser Glu Lys Glu Ile Ile Ser Lys Glu Gln Gly Asn Val Lys Ala
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                                                                       208
 Gln Glu Leu Leu Ala Val Ala Phe Gly Val Lys Val His Thr Phe Arg
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 Gly Pro His Trp Cys Glu Tyr Cys Ala Asn Phe Met Trp Gly Leu Ile
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    Met Val Val Phe Met Thr Tyr Val Thr Leu Pro Phe Phe Ser
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cag Gln	gag Gli	g ct ı Le	a tt u Ph 5	c tt ne Le	g aa u Ly	g tt 's Ph	t gt e Va	g ga l As 10	t ga p Gl	a aa u As	t tgg n Tr	g gaa	a gg u Gl	t to Y Se:	c ctc	: 	524
Lys	Sei	Ly 20	s Ту	r Va	l Ar	g Gl	y Se 25	r As	p Pr	o Vai	l Le	ı Ly: 30	g ct	ı Lei	g gac ı Asp		572
Asp	Asr 35	gg Gl	g aa y As	n Il	t go e Al	t ga a Gl 40	u Gl	a cto u Len	g ago u Se:	c ați r Ile	t cto E Leu 45	aaa Lyi	a tgg	g aca	a cag		620
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Glu	Glu	Val 35	Lys	: Ile	Glu	Val	Leu 40	His	Arg	Pro	gaa Glu	Asn 45	Cys	Ser	Lys.		201
Thr	Ser 50	Lys	Lys	Gly	gac Asp	Leu 55	cta Leu	aat Asn	gcc Ala	cat His	tat Tyr 60	gac Asp	ggc Gly	tac Tyr	ctg Leu		249
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Ile	Ser	His	Gly	Phe 20	Ala	Arg	Gly	Val	Arg 25	Arg	ggt Gly	Val	Ala	Ile 30	gtg Val	•	96
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Met Val Ala Met Ala Ala -30	
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Gly Pro Ser Gly Cys Leu Val Pro Ala Phe Gly Leu Arg Leu Leu Leu	•
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Glu Ala Cys Arg Glu Leu Gly Phe Ser Ser Asn Leu Leu Cys Ser Ser	3,7
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Cys Asp Leu Leu Gly Gln Phe Asn Leu Leu Gln Leu Asp Pro Asp Cys	
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WO 99/53051 PCT/IB99/00712
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-15 -10 -5

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ctt ggg ggg cct gcc tgc ctg aag acc cag gaa cac ccc agc tgc cca	96
Leu Gly Gly Pro Ala Cys Leu Lys Thr Gln Glu His Pro Ser Cys Pro 1 5 10	
gga ccc agg gaa ctg gaa gcc agc aaa gtt gtc ctc.ctg ccc agt tgt	144
Gly Pro Arg Glu Leu Glu Ala Ser Lys Val Val Leu Leu Pro Ser Cys	
15 20 25 30	
ccc gga gct cca gga agt cct ggg gag aag gga gcc cca ggt cct caa	192
Pro Gly Ala Pro Gly Ser Pro Gly Glu Lys Gly Ala Pro Gly Pro Gln	
35 40 45	
ggg cca cct gga cca cca ggc aag atg ggc ccc aag ggt gag cca gga	240
Gly Pro Pro Gly Pro Pro Gly Lys Met Gly Pro Lys Gly Glu Pro Gly	
50 55 60	
gat cca gtg aac ctg ctc cgg tgc cag gaa ggc ccc aga aac tgc cgg	288
Asp Pro Val Asn Leu Leu Arg Cys Gln Glu Gly Pro Arg Asn Cys Arg	
65 70 75	
gag ctg ttg agc agg gcg cca cct tgagcggctg gtamcatctg tgcctacctg	342
Glu Leu Leu Ser Arg Ala Pro Pro	•
80 85	
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Pro Ser Xaa Ser Ala Val Val Leu Pro Ser Thr Pro Gln Ala Ser Ala	
-15 -10 -5	
aat cca tca tct ccc tat aca aat agt tcc cga aaa caa cct atg agt	154
Asn Pro Ser Ser Pro Tyr Thr Asn Ser Ser Arg Lys Gln Pro Met Ser	
1 5 10 15	
gca aca ctt aga gaa aga tta agg aaa aca aga ttt tca ttt aat tcc	202
Ala Thr Leu Arg Glu Arg Leu Arg Lys Thr Arg Phe Ser Phe Asn Ser	
20 25 30	
tot nac aat gtg gtg aac gtc tta aag tagagagtga agaasatgat	249
Ser Xaa Asn Val Val Asn Val Leu Lys	442
35 40	
cagacetttt cagagaacee ageatettee acagaggraa actgtttggr atteaaagaa	200
	309 369
agtitaaamc atatagroag tgatttgaag aaaatacaaa titgnaaaat actitgaaga	369
atctcaatgt ctgtgaatct cagtcacttg attctggatc atgcagtg	
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  tettggatgg acettgeact etagaaggga ca atg gae tte tgg ett tgg eca
                                                                         120
                                                                         173
                                      Met Asp Phe Trp Leu Trp Pro
  ctt tac ttc ctg cca gta tcr ggg gcc ctg agg atc ctc cca gaa gta
  Leu Tyr Phe Leu Pro Val Ser Gly Ala Leu Arg Ile Leu Pro Glu Val
                                                                        221
  aag gta gag ggg gag ctg ggc gga tca gtt acc atc aag tgc cca ctt
 Lys Val Glu Gly Glu Leu Gly Gly Ser Val Thr Ile Lys Cys Pro Leu
                                                                        269
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 Pro Glu Met His Val Arg Ile Tyr Leu Cys Arg Glu Met Ala Gly Ser
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                          30
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 Gly Thr Cys Gly Thr Val Val Ser Thr Thr Asn Phe Ile Xaa Ala Glu
                                                                        365
                     45
 tac aag ggc cga gtt act ctg aga gca ata ccc acg caa gaa tct gtt
 Tyr Lys Gly Arg Val Thr Leu Arg Ala Ile Pro Thr Gln Glu Ser Val
                                                                        413
                 60
                                     65
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 Pro Ser Gly Gly Asn Thr Ala Asp Arg Lys
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                                                                       49
gtg gcc gtt acg gcc gaa aag atg gcg gtc ttg gca cct cta att gct
Val Ala Val Thr Ala Glu Lys Met Ala Val Leu Ala Pro Leu Ile Ala
                                                                       97
                    -15
                                        -10
                                                             ~ 5
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tac ctt ctg tcg Tyr Leu Leu Ser	scc ctg ctc Xaa Leu Leu	tct gmt gcc	ttc cta ctc	gtg agg maa 19	3
. 15		20	25	1	
ctg ccg ccg ctc Leu Pro Pro Leu 30	Cys His Gly 35	Leu Pro Thi	Gln Arg Glu )	Kaa Gly Asn	1
ccg tcr wsa ytt Pro Ser Xaa Xaa 45	tgactgggtg ;	agcctcccgc <u>c</u>	gtgttagtac ccc	gcgacsk 29	)3
tgactgtscc tgcc cctgakgttc cgag tcgagtctaa actt caacggccca acag	cctgta gcggad tgtgtt taaga1	cttag agacta tggga aaacgg	ittaw ktgcagggt Jaaca tgttagtco	c cgaaccatca 41 pt agcccatgca 47	3
			teet teetgeete	a ccacegag 33	_
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		•	Met Ala Gli -1	n Leu Trp	•
ctg tcc tgc ttc Leu Ser Cys Phe -10	Leu Leu Pro	gcc ctc gtg Ala Leu Val -5	gtg tct gtg ge Val Ser Val A	ca gcc aac 282 la Ala Asn	2
gtg gcc cck wag	ttc cta gcc a	aac atg acg	tca gtg atc ci	g cct gag 330	0
Val Ala Pro Xaa : 5	Phe Leu Ala 1	Asn Met Thr	Ser Val Ile Lo	eu Pro Glu 20	
gac tgc ctg tgg	gtg ccc agg	cct tct ggt	tgg tagcg	368	В
Asp Cys Leu Trp	vai Pro Arg i 25	Pro Ser Gly 30	Trp		
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<211> 469				÷	
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PCT/IB99/00712

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412

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Met Val Ala Trp Arg Ser Ala Phe Leu Val Cys Leu

-15

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Ala Phe Ser Leu Ala Thr Leu Val Gln Arg Gly Ser Gly Asp Phe Asp
-5

gat ttt aac ctg gag gat gca gtg aaa gaa act tcc tca gta aag cag
208

Asp Phe Asn Leu Glu Asp Ala Val Lys Glu Thr Ser Ser Val Lys Gin
10 20 25

60 65
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Met Ala Asp Pro Asp Pro Arg Tyr Pro Arg Ser Ser Ile
-50 -45
gag gac gac ttc aac tat ggc agc agc gtg gcc tcc gcc acc gtg cac 159
Glu Asp Asp Phe Asn Tyr Gly Ser Ser Val Ala Ser Ala Thr Val His

-40 -35 -30 -25
atc cga atg gcc ttt ctg aga aaa gtc tac agc att ctt tct ctg cag 207
Ile Arg Met Ala Phe Leu Arg Lys Val Tyr Ser Ile Leu Ser Leu Gln

-20 -15 -10
gtt ctc tta act aca gtg act tca aca gtt ttt tta tac ttt gag tct 255
Val Leu Leu Thr Thr Val Thr Ser Thr Val Phe Leu Tyr Phe Glu Ser

gta cgg aca ttt gta cat gag agt cct gcc tta att ttg ctg ttt gcc 303
Val Arg Thr Phe Val His Glu Ser Pro Ala Leu Ile Leu Leu Phe Ala
10 15 20

ctc gga tct ctg ggt ttg att ttt gcg ttg ayt tta aac aga cat aag

151

Leu Gly Ser Leu Gly Leu Ile Phe Ala Leu Xaa Leu Asn Arg His Lys

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                                                                       117
                                                           Met Ser
tcc cag aaa ggc aac gtg gct cgt tcc aga cct cag aag cac cag aat
                                                                       165
Ser Gln Lys Gly Asn Val Ala Arg Ser Arg Pro Gln Lys His Gln Asn
             -50
                                 -45
acg ttt agc ttc aaa aat gac aag ttc gat aaa agt gtg cag acc aag
                                                                       213
Thr Phe Ser Phe Lys Asn Asp Lys Phe Asp Lys Ser Val Gln Thr Lys
                             -30
age atg aat aat ett tea tit agt gag eta tgt tge ete tie tge tgt
                                                                       261
Ser Met Asn Asn Leu Ser Phe Ser Glu Leu Cys Cys Leu Phe Cys Cys
    -20
                         -15
                                             -10
cca cct tgt cca ggg aag att gct tca aaa tta gcg ttt ttg cca cct
                                                                       309
Pro Pro Cys Pro Gly Lys Ile Ala Ser Lys Leu Ala Phe Leu Pro Pro
gat cca act tac aca ctg atg tgt gat gaa agc gga agc gtt gga ctt
                                                                       357
Asp Pro Thr Tyr Thr Leu Met Cys Asp Glu Ser Gly Ser Val Gly Leu
                                 20
tac atc tgt ctg aac gag cag act ggc agt att ctt cta gag aaa aag
                                                                       405
Tyr Ile Cys Leu Asn Glu Gln Thr Gly Ser Ile Leu Leu Glu Lys Lys
                            35
atg cta ttg agt gtt tca tgactagaac cagtaaaggc aacagaattg
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Met Leu Leu Ser Val Ser
cttgtatgtt tgtacgttgt tcacccaatg cgaaatacac tttactcttc t
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                                                                       116
                                              Met Arg Asn Lys Lys
att ctc aag gag gac gag ctc ttg agt gag acc caa caa gct gct ttt
                                                                      164
Ile Leu Lys Glu Asp Glu Leu Leu Ser Glu Thr Gln Gln Ala Ala Phe
        -55
                            -50
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His Gln Ile Ala Met Glu Pro Phe Glu Ile Asn Val Pro Lys -40 -35 -30	212
agg aga aat ggg gtg aac ttc tcc cta gct gtg gtg gtc atc tac ctg Arg Arg Asn Gly Val Asn Phe Ser Leu Ala Val Val Val Ile Tyr Leu -25 -20 -15 -10	260
atc ctg ctc acc gct ggc gct ggg ctg ctg gtg gtc caa gtt ctg aat  Ile Leu Leu Thr Ala Gly Ala Gly Leu Leu Val Val Gln Val Leu Asn  -5  1  5	308
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ctg gcg gct gag gac agc ccg tcc ttc tcc ttg ctg cag tca gca cac Leu Ala Ala Glu Asp Ser Pro Ser Phe Ser Leu Leu Gln Ser Ala His	404
cct gga gaa cac ctg gct cag ggt gca tcg agg ctg cag tcc tgc agg Pro Gly Glu His Leu Ala Gln Gly Ala Ser Arg Leu Gln Ser Cys Arg 40 45 50 55	452
ccc aac tca cct ggg tcc gcg tca sca tgagcacttg ctgcagcggg Pro Asn Ser Pro Gly Ser Ala Ser Xaa 60	499
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-45 -40 -35  tcc cga gat gct gct cgc tcc cgc cgg gga aaa gaa aac ttt gag ttc  Ser Arg Asp Ala Ala Arg Ser Arg Arg Gly Lys Glu Asn Phe Glu Phe	149
-45 -40 -35  tcc cga gat gct gct cgc tcc cgc cgg gga aaa gaa aac ttt gag ttc  Ser Arg Asp Ala Ala Arg Ser Arg Arg Gly Lys Glu Asn Phe Glu Phe -30 -25 -20  tat gaa ttg gcc aag ttg ttg cct ctt cct gca gcc att acc agc cag  Tyr Glu Leu Ala Lys Leu Leu Pro Leu Pro Ala Ala Ile Thr Ser Gln	149 197
-45 -40 -35  tcc cga gat gct gct cgc tcc cgc cgg gga aaa gaa aac ttt gag ttc  Ser Arg Asp Ala Ala Arg Ser Arg Arg Gly Lys Glu Asn Phe Glu Phe -30 -25 -20  tat gaa ttg gcc aag ttg ttg cct ctt cct gca gcc att acc agc cag	•
-45	197
-45	197 245

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	agc cac att ttg cag tcc tgg atg gct ttg tat ttg cac taaatcagga Ser His Ile Leu Gln Ser Trp Met Ala Leu Tyr Leu His 70 75	438
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	-20 -15 ctg tct gtc tgt tcc acg gat gta acc aca gca cac gcg tgg ctc acg Leu Ser Val Cys Ser Thr Asp Val Thr Thr Ala His Ala Trp Leu Thr -10 -5 1 5	159
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                                                                    291
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          -45
                             -40
                                                 -35
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                                                                    339
Thr Leu Trp Glu Gly Ala Arg Gly His Arg Gln Ile Ser Val Ser Pro
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                                           -20
387
Trp Asn Ile Cys Cys Ala Ala Ala Ala Ala Ala Ala Gly Ser Arg
-15
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Arg	Leu	Gly	Thr	Pro -30	Gln	Gln	Ile	Ala	-25		Arg	Glu	Gly	Asp -20	ctc		154
Leu	Thr	Lys	Glu -15	Arg	Leu	Cys	Cys	Gly -10	Leu	tcc. Ser	Met	Phe	Glu -5	Val	Ile		202
Leu	Thr	Arg 1	Ile	Arg	Ser	Tyr 5	Leu	Gln	Asp	ccc Pro	Ile 10	Trp	Arg	Gly	Pro		250
Pro 15	Pro	Thr	Asn	Gly	Val 20	Met	His	Va'l	Asp	gag Glu 25	Cys	Val	Glu	Phe	His 30		298
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Asn	Glu	Phe	Thr 50	Ala	Glu	Gln	Cys	Phe 55	Gly		Gly	Leu	Asn 60	Trp	Ala		394
Gly	Ser	Pro 65	Xaa	Leu	Ser	Cys	Xaa 70	Ala	Ser	agc Ser	Val	Ala 75	Leu	Thr	tgt Cys		442
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										ggc				Met	Ala -70		57
Leu	Val	Pro (	Cys (	31n \ -65	/al :	Leu i	Arg i	Met	Ala -60	atc Ile :	Leu	Leu	Ser	Tyr -55	Cys		105
tct Ser	atc Ile	Leu (	tgt a Cys <i>l</i> -50	aac t Asn 1	ac a	aag ( Lys 1	Ala :	atc Ile -45	gaa Glu	atg Met	ccc Pro	Ser	cac His (	cag Gln	acc Thr		153
	Gly (					he l				att d	Asp						201
Ala					le (					gat o Asp 1							249

His Ile Ser Phe Pro Ala Leu Thr Gly Ser Gln Leu Leu Gly Asp Thr -15 -10 ate eec ega eet eac ett eea eet ace gea gee tge tageetttee 296 Ile Pro Arg Pro His Leu Pro Pro Thr Ala Ala Cys gggagaaaag gcatccttac ctctggttga aggtctcggg gcctcccct ctgcatccgg 356 accetetece cateceagee teccatgeea aggecegeet tgteagteae tteettttgt 416 catcggcttg gcaaacggga gagaaaacag agcttcatgg gaaacagcgg caacagtggt 476 cccatacacc tttccccaag ttggagctag gcctggggcc ccagcccatg gygccccggg 536 agetecetae etgetecats tgeetggaga ggttgegega ecceatetsg ytggaatgt 595

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			agg Arg -5												ctt Leu	149
			tcc Ser													197
			gat Asp													245
Asp	Āsp	Val	rat Xaa	Pro 45	Val	Thr	Lys	Glu	Lys 50	Gly	Gly	Pro	Arg	Gly 55	Pro	293
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			gcg Ala													213
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Ile	Leu	Gly	act Thr 1	Gly	Leu	Leu	Trp 5	Leu	Pro	Gly	Gly	Ile 10	Lys	Leu	Phe	309
			tat Tyr													357

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40 atg tca agt gga att tgg cag aga ggc aaa gaa gaa gga gtt atg

315

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ccg ctg ggc gca cgg a Pro Leu Gly Ala Arg 7 25	aca gcc tcc cac at Thr Ala Ser His Me 30	g acc aag gac at t Thr Lys Asp Mo 35	g ttc ccg t Phe Pro	150
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tat aat atg cgt gtg g Tyr Asn Met Arg Val C 55	gaa gac tac gaa cc Glu Asp Tyr Glu Pro 50	t tac ccg gat ga Tyr Pro Asp As 65	at ggc atg sp Gly Met 70	246
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Cys Val Trp Val Cys Val Tyr Thr Val Glu Ser Lys Leu Glu Asn Ser	102
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Ala Leu His Gly Gly Met Lys Thr Leu Leu Pro Trp Thr Ala Arg Ala	
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Ser Arg Ser Pro	333
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Arg Glu Lys Leu Thr Pro Glu Gln Leu His Ser Met Arg Gln Ala Glu
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Leu Pro Ser Gly Arg Arg Ser Tyr His Gly Glu Pro Gly Thr Ser
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tgaccggcct aggcatcggg gccctggtgt tggctattta tggttacacc ttctactcga
                                                                      377
tttcccagga gcgtttccta gatgagctag aagacgaggc caaagctgcc cgagcccgag
                                                                      437
ctctggcaag ggcgtcaggg tcctaatctg gatgggtatt gatcatgtcc aacctgctgg
                                                                      497
ageceettea catggtggat gatgeceeat gaccetgtga gaaattgaat cetgeteaca
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acattgttgg ccttcttact aacctnngac ctgattgagc ccaagaaacc agggasttac
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gcatttggcc aa
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aaccaaaggg aaaagccacc ttcccaggca cagccataac atccacctca ctcaactgct
                                                                      120
tgtcaagttc accaccaaca cagaggggc tcagataatc aagaaaca atg tcg agt
                                                                      177
                                                      Met Ser Ser
gat gat aaa agt aaa toa aat gac coc aag act gag coc aag aac tgc
                                                                      225
Asp Asp Lys Ser Lys Ser Asn Asp Pro Lys Thr Glu Pro Lys Asn Cys
gat ccc aag tgt gaa caa aag tgt gag tcc aaa tgc cag ccc agc tgt
                                                                      273
Asp Pro Lys Cys Glu Gln Lys Cys Glu Ser Lys Cys Gln Pro Ser Cys
20
                                         30
                                                             35
tta aag aag ctg ctg caa cgc tgt ttc gaa aag tgc cca tgg gaa aag
                                                                      321
Leu Lys Lys Leu Leu Gln Arg Cys Phe Glu Lys Cys Pro Trp Glu Lys
tgt cca gca cca ccc aag tgc ctg ccc tgc ccc tcg cag tct cct tca
                                                                      369
Cys Pro Ala Pro Pro Lys Cys Leu Pro Cys Pro Ser Gln Ser Pro Ser
tcc tgc cct ccc cag ccc tgc acc aag ccc tgt cct cct aaa tgc cct
                                                                      417
Ser Cys Pro Pro Gln Pro Cys Thr Lys Pro Cys Pro Pro Lys Cys Pro
tca tcc tgc cca cat gct tgc cca mct ccc tgc cct ccc cca gag
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Ser Ser Cys Pro His Ala Cys Pro Xaa Pro Cys Pro Pro Pro Glu
    85
                        90
tgaggcactg tgggc
                                                                      477
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gggtwtgggg aaaggaaggc tggcttggcg agagggcagg tttgcqqqct ttcqcccct
                                                                      120
tttccaaaga ccaacaaaga gtccttcccc aactcccaac tcaacccctt ttggaact
                                                                      178
atg tgt ggt ggt tgg gac cet gtg geg cat cet tgt ege teg tgt cet
                                                                      226
Met Cys Gly Gly Trp Asp Pro Val Ala His Pro Cys Arg Ser Cys Pro
tet cat gee egg ega ege gte ttt gtg gta aeg eee tge tge eat ete
                                                                      274
Ser His Ala Arg Arg Arg Val Phe Val Val Thr Pro Cys Cys His Leu
                                25
ttt tct tct cta tgc gag gat ttg gac tgg cag tgagaataag agacaacgat
                                                                      327
Phe Ser Ser Leu Cys Glu Asp Leu Asp Trp Gln
teaegtetae tttetaggat gaetteeatg tgeteeatet egegegteee tgaqeatqtt
                                                                      387
qaatttccaa atcctaaata agccgcgcgg tgtaqtttgt attatqttqc qtttctcttt
                                                                      447
ctgcttttcc tcgccctttc tccatcatcc tttaggctct acagagtgaa ggtttaaatc
                                                                      507
caaggtcatg gcaaaacatc tgaagttcat cgccaggact gtgatggtac aggaagggaa
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cgtggaaagc gcatacagg
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<211> 559

<212> DNA

<213> Homo sapiens

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<400:	> 80	4														,	•
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ggcct	tgag	ga	gccc	atc	atg	gcg	acg	ccc	cct	aaq	caa	caa	aca	ata	gag		110
		· -			Met 1	Ala	Thr	Pro	Pro 5	Lys	Arg	Arg	Ala	Val	Glu		
gcċ a	acg	ggg	gag	aaa	gtg	cto	cqc	tac	aaq	acc	ttc	ato	agt		ata		15
Ala 7	Chr	Gly	Glu 15	Lys	Val	Leu	Arg	Tyr 20	Glu	Thr	Phe	Ile	Ser 25	Asp	Val		
ctg c	cag	cgg	gac	ttg	cga	aag	gtg	ctg	gac	cat	cga	gac	aag	qta	tat		206
Leu (	3ln	Arg 30	Asp	Leu	Arg	Lys	Val 35	Leu	Asp	His	Arg	Asp	Lys	Val	Tyr		
gag c	ag	ctg	gcc	aaa	tac	ctt	caa	ctg	aga	aat	gtc	att	gaq	cga	ctc		.254
Glu G	31n 15	Leu	Ala	Lys	Tyr	Leu 50	Gln	Leu	Arg	Asn	Val 55	Ile	Glu	Arg	Leu		
cag g	jaa	gct	aag	cac	tcg	gag	tta	tat	atg	çag	gtg	gat	ttg	ggc	tgt		302
Gln G 60	Slu	Ala	Lys	His	Ser 65	Glu	Leu	Tyr	Met	Gln 70	Val	Asp	Leu	Gly	Cys 75	1	-
aac t	tc	ttc	gtt	gac	aca	gtg	gtc	çса	gat	act	tca	cgc	atc	tat	gtg		350
Asn P				80					85					90			
gcc c	tg:	gga	tat	ggt	ttt	ttc	ctg	gag	ttg	aca	ctg	gca	gaa	gct	ctc		398
Ala L			95					100					105				
aag t	tc	att	gat	cgt	aag	agc	tct	ctc	ctc	aca	gag	ctc	agc	aac	agc		446
Lys P		110					115					120					
ctc a	CC (	aag	gac	tcc	atg	aat	atc	aaa	gcc	cat	atc	cac	atg	ttg	cta		494
_	25					130					135						
gag g	gg	ctt	aga	gaa	cta	caa	ggc	ctg	cag	aat	ttc	cca	gag	aag	cct		542
Glu G	ly :	Leu	Arg	Glu		Gln	Gly	Leu	Gln	Asn	Phe	Pro	Glu	Lys	Pro		
140					145					150					155		
cac c His H		tgac	ttct	tc c	3												559
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aaaca	cato	cc a	agct	taag	a cg	gtga	iggto	ago	ttca	cat	tctc	agga	ac t	ctcc	ttctt		60
tgggt	ctg	gc t	gaag	ttga	g ga	tctc	ttac	tct	ctag	gcc	acgg	gaatt	aa d	ccga	gcagg		120
Met	Glu	g gc	c tc a Se	r Al	t ct a Le	c ac u Th	r Se	a to r Se	r Al	a Va	g ac	c ag	jt gt er Va	al Al	c aaa a Lys		169
1				5					10					15			
gtg g Val V	al A	۱rg ا	grg ( Val 1 20	gcc Ala	Ser	ggc Gly	Ser	Ala	gta Val	gtt Val	t t g Leu	ccc Pro	Leu	gcc Ala	agg Arg		217
att ~	ct -			ato	att.	OG =		25	a+-	aa+	a+~		30	- t-			
att go Ile A	la 7	Chr V	Val V	Val	Ile	Gly	gga Gly 40	Val	Val	Ala	Val	Pro	Met	Val	Leu		265
agt g	_	-	ac t	itc .	act (			aas	atc	מככ	tea		tee	ata	ac -		212
Ser A.																	313

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<222> 152..346

<221> misc\_feature
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<222> 149..247

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Ile Arg Gln Asp His Ile 110

566

gtcggatgaa gaggaggaaa ggggtgatgg aggggcagag cctggagcct gcagctagca gtgggcccct gcctacagac tgaccacgct ggctattctc cacatgagac cackagccca 746 mknnagagcc tgtcgggaga agaccagact ctttacttgc agtnnracca gaggtgggaa 806 ngatggtggg attgtgtacc tttctaaga 835 <210> 811

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<222> 373

<223> n=a, g, c or t

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<210> 812

<211> 90

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -14..-1

<400> 812

Met Leu Leu Pro Leu Leu Leu Leu Pro Met Cys Trp Ala Val Glu -10

Val Lys Arg Pro Arg Gly Val Ser Leu Thr Asn His His Phe Tyr Asp

Glu Ser Lys Pro Phe Thr Cys Leu Asp Gly Ser Ala Thr Ile Pro Phe 25

Asp Gln Val Asn Asp Asp Tyr Cys Asp Cys Lys Asp Gly Ser Asp Glu

Pro Gly Thr Ala Ala Cys Pro Asn Gly Ser Phe His Cys Thr Asn Thr 55

Gly Tyr Lys Pro Leu Tyr Ile Pro Ser Asn

<210> 813

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<213> Homo sapiens
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 <222> -16..-1
<400> 813
Met Arg Leu Ser Leu Pro Leu Leu Leu Leu Leu Gly Ala Trp Ala
  -15
                        -10
Ile Pro Gly Gly Leu Gly Asp Arg Ala Pro Leu Thr Ala Thr Ala Pro
Gln Leu Asp Asp Glu Glu Met Tyr Ser Ala His Met Pro Ala His Leu
            20
                                25
Arg Cys Asp Ala Cys Arg Ala Val Ala Tyr Gln Val Ser Pro Ser Pro
                            40
Leu Ser Pro Ala Leu Leu Thr Pro Leu Leu Lys Pro Ala Pro Thr Gly
                         55
<210> 814
<211> 67
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1
<400> 814
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp
                            -15
Leu Arg Gly Ala Arg Cys Gly Val Gln Met Thr Gln Phe Pro Leu Ser
                       1
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Thr Ser
                15
                                    20
His Ile Ile Asn Ile Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
                                35
Ala Pro Trp
        45
<210> 815
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 815
Met Ala Ala Ala Leu Trp Gly Phe Phe Pro Val Leu Leu Leu Leu
                                -15
Leu Ser Gly Asp Val Gln Ser Ser Glu Val Pro Gly Ala Ala Ala Glu
       - 5
Gly Ser Gly Gly Ser Gly Val Gly Ile Gly Xaa Arg Phe Lys Ile Glu
10
                   15
Gly Leu
<210> 816
<211> 84
<212> PRT
<213> Homo sapiens
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 <221> SIGNAL
 <222> -22..-1
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                            -15
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Leu Xaa Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Val Leu
Pro Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln
Ser Ile Gly Ser Tyr Leu Asn Trp Tyr Gln His Lys Pro Gly His Ala
                                35
Pro Arg Leu Leu Ile Tyr Ala Ala Thr Thr Leu Ser Arg Gly Gly Pro
Ala Arg Phe Ser
   60
<210> 817
<211> 72
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1
<400> 817
Met Ala Ala Ser Arg Trp Ala Arg Lys Ala Val Val Leu Leu Cys Ala
                            -25
Ser Asp Leu Leu Leu Leu Leu Leu Leu Pro Pro Pro Gly Ser Cys
                        -10
Ala Gly Arg Arg Ser Pro Xaa Thr Pro Asp Glu Ser Thr Pro Pro Pro
                5
                                    10
Arg Lys Lys Lys Asp Ile Arg Asp Tyr Asn Asp Ala Asp Met Ala
           20
Arg Leu Leu Glu Gln Gly Glu Gly
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<210> 818
<211> 127
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 818
Met Glu Leu Gly Leu Cys Trp Val Leu Leu Leu Ala Leu Leu Glu Gly
                -15
Val Gln Cys Asp Val Glu Leu Val Glu Ser Gly Gly Leu Val Gln
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Phe
                       20
Ser Thr Tyr Glu Met His Trp Ile Arg Gln Ala Pro Gly Lys Gly Pro
Glu Trp Val Xaa Tyr Val Ser Gly Gly Gly Gly Thr Xaa Xaa Asn Ala
               50
Xaa Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Asn Ser
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Phe Val Tyr Leu Gln Met Asp Ser Leu Arg Val Glu Asp Thr Ala Leu

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Tyr Tyr Cys Ala Arg Xaa Asp Tyr Asp Phe Trp Ser Gly Tyr Tyr
    95
                                             105
<210> 819
<211> 28
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 819
Met Ala Trp Thr Pro Leu Leu Leu Leu Leu Ser His Cys Thr Gly
                -15
Ser Leu Ser Gln Pro Val Leu Thr Gln Pro Arg Gly
<210> 820
<211> 122
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 820
Met Glu Phe Gly Leu Asn Trp Val Phe Leu Val Ala Leu Leu Arg Gly
                -15
                                    -10
Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Val Val Gln
Pro Gly Thr Ser Leu Thr Leu Ser Cys Ala Gly Ser Gly Phe Ser Phe
                        20
Ser Asp Tyr Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
Glu Trp Val Ala Val Ile Ser His Asp Gly Asn Asn Lys Tyr Tyr Gly
Gly Ser Met Lys Gly Arg Val Thr Ile Ser Arg Asp Asn Ser Arg His
Thr Val Ser Leu Gln Met Ser Ser Leu Gly Pro Glu Asp Thr Ala Val
Tyr Tyr Cys Ala Lys Asp Arg Thr Gly Gly
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<210> 821
<211> 93
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 821
Met Lys Leu Leu Trp Phe Phe Leu Leu Leu Leu Ala Ala Pro Arg Trp
Val Leu Ser Gln Val Gln Leu Val Xaa Ser Gly Pro Gly Leu Val Lys
Pro Ser Gly Thr Leu Ser Leu Thr Cys Thr Val Xaa Gly Xaa Xaa Ile
Thr Asn Tyr Tyr Trp Ser Xaa Ile Arg Gln Ser Pro Gly Lys Gly Leu
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35

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436
Glu Trp Ile Gly Thr Ile Tyr Tyr Ser Gly Ser Ala Asp His Asn Pro
 Ser Leu Arg Ser Arg Ala Thr Ile Ser Leu Asp Thr Arg
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<210> 822
 <211> 48
<212> PRT
 <213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 822
Met Ala Ser Leu Gly Leu Leu Leu Leu Xaa Leu Leu Thr Ala Leu Pro
-20
                    -15
                                        -10
Pro Leu Trp Ser Ser Ser Leu Pro Gly Leu Asp Thr Ala Glu Ser Lys
                                5
Ala Thr Xaa Ala Asp Leu Ile Leu Ser Ala Leu Glu Arg Ala Thr Gly
        15
                            20
                                                25
<210> 823
<211> 96
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -28..-1
<400> 823
Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu
           -25
                             -20
                                                    -15
Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys
       -10
                            - 5
Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp
                   10
Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala
                25
Ile Pro Gly Ile Arg Gly Pro Lys Gly Gln Lys Gly Glu Pro Gly Leu
            40
                                45
Pro Gly His Pro Gly Lys Asn Gly Pro Met Gly Pro Pro Gly Met Pro
                            60
<210> 824
<211> 143
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 824
Met Asp Cys Thr Trp Arg Ile Leu Leu Leu Val Ala Ala Ala Thr Gly
                -15
                                   -10
Thr His Ala Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Lys
Pro Gly Ala Ser Val Lys Val Ser Cys Gln Val Ser Gly Tyr Asn Val
                       20
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Val Glu Leu Ser Ile His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu

15

20

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.Glu Trp Met Gly Gly Phe Asp Leu Glu Ser Gly Glu Thr Ile Tyr Ala
 Gln Arg Phe Gln Gly Arg Ile Thr Met Thr Glu Asp Ser Ser Ser Asp
             65
                                  70
 Thr Ala Phe Met Glu Leu Ile Ser Leu Arg Pro Glu Asp Ala Ala Val
                              85
 Tyr Tyr Cys Ala Thr Ile Arg Leu Pro Val Val Leu Phe Phe Ala Ala
                         100
                                              105
 Ser Gly Ala Arg Glu Pro Trp Ser Pro Ser Pro Gln Xaa Pro Arg
                     115
                                          120
 <210> 825
 <211> 37
 <212> PRT
 <213> Homo sapiens
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<221> SIGNAL
<222> -18..-1
<400> 825
Met Trp Leu Pro Leu Val Leu Leu Leu Ala Val Leu Leu Leu Ala Val
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Leu Cys Lys Val Tyr Leu Gly Leu Phe Ser Gly Ser Ser Pro Asn Pro
Phe Ser Glu Glu Arg
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<210> 826
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 826
Met Glu Leu Ala Leu Arg Arg Ser Pro Val Pro Arg Trp Leu Leu Leu
                    -20
                                         -15
Leu Pro Leu Leu Gly Leu Asn Ala Gly Ala Val Ile Asp Trp Pro
                - 5
Thr Glu Glu Gly Lys Glu Val Trp Asp Tyr Val Thr Val Arg Lys Asp
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                            15
Ala Tyr Met
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<210> 827
<211> 131
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -19..-1
<400> 827
Met Ala Trp Thr Pro Leu Phe Leu Phe Leu Leu Thr Cys Cys Pro Gly
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                                    -10
Ser Asn Ser Gln Ala Val Xaa Thr Gln Glu Pro Leu Thr Asp Cys Val
Pro Arg Xaa Thr Val Thr Leu Thr Cys Gly Ser Ser Ile Gly Ala Val
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438
 Thr Asn Gly His Phe Pro Tyr Trp Phe Gln Gln Lys Pro Gly Gln Ala
                     35
                                        40
 Pro Arg Thr Leu Ile Ser Asp Thr Phe Asn Arg Gln Ser Ser Thr Pro
                                     55
Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Val Leu Thr Leu
                                 70
 Ser Asp Ala Gln Pro Asp Asp Glu Ala Glu Tyr Tyr Cys Val Leu Ser
                             85
                                                90
Tyr Ser Gly Gly Arg Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val
                        100
Leu Ser Gln
110
<210> 828
<211> 25
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -21..-1
<400> 828
Met Gln Ala Cys Met Val Pro Gly Leu Ala Leu Cys Leu Leu Gly
                        -15
Pro Leu Ala Gly Ala Lys Pro Val Gln
<210> 829
<211> 79
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 829
Met Pro Ser Tyr Lys Val Cys Gly Val Phe Cys Leu Phe Val Cys Leu
            -20
                                -15
Phe Leu Ser Gln Ser Phe Ala Phe Val Leu Gln Ala Gly Val Gln Trp
Arg Asp Leu Cys Ser Leu Gln Pro Gln Leu Pro Arg Phe Gly Pro Ser
                   15
                                        20
Ser Cys Leu Ser Leu Pro Ser Gly Trp Asp Cys Arg Arg Pro Pro Pro
Arg Leu Ala Asn Ser Cys Val Phe Gly Gly Asp Gly Val Ser Pro
                                50
<210> 830
<211> 59
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 830
Met Gly Thr Gln Glu Gly Trp Xaa Leu Leu Cys Leu Ala Leu Ser
  -20
                       -15
                                           -10
```

Gly Ala Ala Glu Thr Lys Pro His Pro Ala Glu Gly Gln Trp Arg Ala

<220>

439 Val Xaa Val Val Leu Asp Xaa Phe Leu Val Lys Asp Xaa Ala His Arg 20 Gly Ala Leu Ala Ser Ser Glu Asp Arg Ala Arg <210> 831 <211> 126 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 831 Met Ser Met Leu Val Val Phe Leu Leu Leu Trp Gly Val Thr Trp Gly -10 -15 Pro Val Thr Glu Ala Ala Ile Phe Tyr Glu Thr Gln Xaa Ser Leu Trp 10 Ala Glu Ser Glu His Xaa Leu Lys Thr Leu Gly Gln Cys Asp Ala Asp 25 Val Pro Gly Pro Pro Gly Asp Ser Arg Leu Pro Ala Val Gln Glu Trp · 35 40 Cly Ala Gln Glu Pro Val His Leu Asp Ser Pro Ala Ile Lys His Gln 55 Phe Leu Leu Thr Gly Asp Thr Gln Gly Arg Tyr Arg Cys Arg Ser Gly 70 75 Leu Ser Thr Gly Trp Xaa Gln Leu Ser Lys Leu Leu Glu Leu Thr Gly 85 90 Pro Lys Val Leu Ala Cys Ser Leu Ala Leu Asp Gly Ala Ser 105 <210> 832 <211> 100 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 832 Met Leu Pro Ser Gln Leu Ile Gly Phe Leu Leu Trp Val Pro Ala -15 -10 Ser Arg Gly Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Leu Ser Val 10 Thr Pro Lys Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Xaa Ser Ile 20 25 Gly Ser Ser Leu Tyr Trp Tyr Gln Gln Lys Pro His Gln Ser Pro Lys 35 40 Leu Val Ile Lys Tyr Ala Ser Gln Ser Phe Ser Gly Val Ser Ser Arg 50 55 Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser 70 Leu Glu Pro Gly 80 <210> 833 <211> 115 <212> PRT <213> Homo sapiens

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440
<221> SIGNAL
<222> -20..-1
<400> 833
Met Glu Lys Ile Pro Val Ser Ala Phe Leu Leu Val Ala Leu Ser
                    -15
                                        -10
Tyr Thr Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala Lys Lys Asp
Thr Lys Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser Arg Gly Trp
                            20
Gly Asp Gln Leu Ile Trp Thr Gln Thr Tyr Glu Glu Ala Leu Tyr Lys
                        35
Ser Lys Thr Ser Asn Lys Pro Leu Met Ile Ile His His Leu Asp Glu
                    .50
                                        55
Cys Pro His Ser Gln Ala Leu Lys Lys Val Phe Ala Glu Asn Lys Glu
                                    70
Ile Gln Lys Leu Ala Glu Gln Phe Val Leu Leu Asn Leu Val Tyr Glu
                                85
Thr Thr Asp
        95
<210> 834
<211> 119
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 834
Met Arg Pro Gly Leu Ser Phe Leu Leu Ala Leu Leu Phe Phe Leu Gly
-20
                    -15
                                        -10
Gln Ala Ala Gly Asp Leu Gly Asp Val Gly Pro Pro Ile Pro Ser Pro
Gly Phe Ser Ser Phe Pro Gly Val Asp Ser Ser Ser Ser Phe Ser Ser
                            20
Ser Ser Arg Ser Gly Ser Ser Ser Arg Ser Leu Gly Ser Gly Gly
                        35
Ser Val Ser Gln Leu Phe Ser Asn Phe Thr Gly Ser Val Asp Asp Arg
                    50
                                        55
Gly Thr Cys Gln Cys Ser Val Ser Leu Pro Asp Thr Thr Phe Pro Val
                65
                                    70
Asp Arg Val Glu Arg Leu Glu Phe Thr Ala His Val Leu Ser Gln Lys
                                85
Phe Glu Lys Glu Leu Ser Lys
     95
<210> 835
<211> 147
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 835
Met Asp Leu Leu His Lys Asn Met Lys His Leu Trp Phe Phe Leu Leu
```

-25 -20 -15 Leu Val Ala Ala Pro Arg Trp Val Arg Ser Gln Val Gln Leu Xaa Glu - 5 Ser Gly Pro Gly Leu Val Lys Pro Ser Gly Thr Leu Ser Leu Ile Cys

```
Gly Val Ser Gly Asp Ser Val Thr Ile Ser Gly Trp Trp Ser Trp Val
                             30
 Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Ser Glu Ile Asp His
                         45
 Gly Gly Asn Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Xaa Ile
                     60
 Ser Leu Asp Lys Ser Lys Asn Lys Phe Ser Leu Arg Leu Thr Ser Val
                 75
                                     80
Thr Ala Ala Asp Thr Ala Met Tyr Xaa Cys Ala Arg Gly Gly Ala Xaa
                                 95
Ser Ser Ser Ala Phe Asp Val Trp Gly Leu Xaa Thr Met Val Ile Ile
        105
                             110
Ser Ser Ala
   120
<210> 836
<211> 139
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 836
Met Asp Ile Leu Cys Ser Thr Leu Leu Leu Leu Thr Val Pro Ser Trp
                -15
                                    -10
Val Leu Ser Gln Val Thr Leu Xaa Glu Ser Gly Pro Ala Leu Val Lys
Ala Thr Gln Thr Leu Arg Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu
Ser Thr Asn Arg Met Arg Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
Ala Leu Glu Trp Leu Ala Arg Ile Asp Trp Asp Asp Tyr Lys Arg Tyr
Ser Thr Ser Leu Lys Thr Arg Val Thr Ile Ser Lys Asp Thr Ser Lys
                                 70
Asn Gln Val Ile Leu Thr Met Thr Asn Val Asp Pro Ala Asp Thr Ala
                            85
Thr Tyr Tyr Cys Ala Arg Leu Ser Thr Ala Ala Thr Pro Gln Phe Phe
                        100
Asp Phe Trp Gly Gln Gly Val Leu Val Ser Val
                    115
<210> 837
<211> 139
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 837
Met Xaa His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
               -15
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
Pro Ser Xaa Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile
                        20
Ser Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu
                   35
```

```
442
Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro
Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln
                                 70
Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
                             85
Tyr Cys Ala Arg Xaa Leu Xaa Tyr Tyr Asp Arg Ser Gly Tyr Phe Arg
                         100
Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Trp Ser
                     115
<210> 838
<211> 136
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 838
Met Lys His Leu Trp Phe Phe Leu Leu Val Ala Ala Pro Arg Trp
                 -15
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
Asp Ser Gly Asn Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys
                    35
Gly Leu Glu Trp Ile Gly Arg Ile Tyr Ser Thr Gly Ser Thr Asn Tyr
Asn Pro Ser Leu Ser Ser Arg Val Gln Ile Ser Leu Asp Thr Ser Lys
                                70
Asn Leu Leu Ser Leu Asn Leu Thr Ser Val Thr Ala Ala Asp Thr Ala
                            85
                                                90 .
Val Tyr Phe Cys Ala Arg Thr Phe Pro Phe Tyr Trp Tyr Leu Asp Leu
                        100
Trp Gly Arg Gly Ile Leu Val Thr
110
<210> 839
<211> 143
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 839
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
                -15
                                    -10
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Arg Leu Val Lys
Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
                        20
Ser Ser Gly Gly Tyr Phe Trp Ser Trp Ile Arg Gln His Pro Gly Arg
                                        40
Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Asn Trp Ser Thr Tyr Tyr
                                    55
Asn Pro Ser Leu Arg Ser Arg Val Thr Met Ser Met Asp Thr Ser Lys
```

Asn Gln Phe Ser Leu Asn Leu Asn Ser Val Thr Ala Ala Asp Thr Xaa

```
80
 Met Tyr Tyr Cys Ala Arg Gly Arg Gly Arg Leu Gly Trp Phe Xaa Xaa
                         100
                                              105
 Xaa Gly Xaa Gly Xaa Pro Gly His Arg Leu Ile Ser Arg Pro Gly
                                          120
 <210> 840
 <211> 111
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
 <222> -19..-1
 <400> 840
 Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
                 -15
                                     -10
 Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
 Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
                         20
 Arg Thr Gly Ser Tyr Tyr Trp Thr Trp Val Arg Gln Pro Pro Gly Lys
                     35
                                         40
Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Thr Gly Asp Thr Tyr Tyr
                50
                                     55
                                                         60
Asn Pro Ser Leu Lys Ser Arg Ile Thr Met Ser Leu Asp Thr Xaa Xaa
            65
                                 70
Asn Gln Phe Xaa Leu Ser Leu Thr Ser Val Thr Val Ala Asp Thr
                             85
<210> 841
<211> 53
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -15..-1
<400> 841
Met Lys Leu Ser Val Cys Leu Leu Leu Val Thr Leu Ala Leu Cys Cys
                    -10
                                        - 5
Tyr Gln Ala Asn Ala Glu Phe Cys Pro Ala Leu Val Ser Glu Leu Leu
                                10
Asp Phe Phe Phe Ile Ser Glu Pro Leu Phe Lys Leu Ser Leu Ala Lys
       20
Phe Asp Ala Pro Arg
   35
<210> 842
<211> 23
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 842
Met Ser Pro Val Leu Leu Val Leu Ser Leu Ser Gln Cys Leu Leu Ser
                       -10
Asp Pro Val Ile Pro Gly Leu
```

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444
<210> 843
<211> 93
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 843
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
                -15
                              -10
Val Leu Ser Gln Val Arg Leu Gln Glu Ser Gly Pro Arg Leu Val Lys
Pro Ser Glu Xaa Leu Ser Leu Thr Cys Ser Val Ser Gly Val Ser Val
                        20
Thr Asn Phe Phe Trp Asn Trp Ile Arg Lys Pro Pro Gly Lys Gly Leu
                    35
                                        40
Glu Trp Leu Gly Tyr Met Ser Tyr Gly Val Ser Thr Asn Tyr His Pro
                50
Ala Tyr Gln Ser Arg Val Ser Ile Ser Ile Asp Thr Trp
<210> 844
<211> 139
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 844
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
                -15
                                    -10
Val Leu Ser Gln Val Gln Leu Gln Glu Ala Gly Pro Arg Leu Val Lys
Pro Ser Glu Ala Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Ser
Ser Asn Tyr Asp Trp Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
                                        40
Glu Trp Ile Gly Tyr Ile Asp Asp Ser Lys Asn Arg Gly Ser Thr Thr
                50
Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Xaa Asp Thr Ser
Lys Xaa Gln Leu Ser Leu Arg Leu Thr Ser Val Thr Xaa Ala Asp Thr
                           85
Ala Val Tyr Tyr Cys Ala Arg Lys Ser Ser Met His Ser Ser Gly Trp
                       100
His Asn Arg Ser Leu Tyr Trp Tyr Phe Asp Pro
<210> 845
<211> 134
<212> PRT
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<213> Homo sapiens

<220>

<221> SIGNAL

<222> -26..-1

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<400> 845
Met Asp Leu Leu His Lys Asn Met Lys Asp Leu Trp Phe Phe Leu Leu
                         -20
                                             -15
Leu Val Ala Ala Pro Arg Trp Val Leu Ser Gln Val Leu Gln Glu Ser
                     -5
Gly Pro Gly Leu Val Lys Pro Ser Gly Thr Leu Ser Leu Thr Cys Ala
                                 15
Val Ser Gly Gly Ser Ile Ile Ser Ser Asn Trp Trp Ser Trp Val Arg
                             30
Gln Thr Pro Gly Lys Gly Leu Glu Trp Ile Gly Glu Ile Tyr Glu Asp
                         45
Gly Ile Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Ile Ile Ser
                     60
Val Asp Lys Ala Lys Asn Gln Phe Ser Leu Lys Met Arg Ser Val Thr
                 75
Ala Ser Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ser Ser Ser Val
            90
                                 95
Arq Thr Asp Tyr Trp Gly
        105
<210> 846
<211> 144
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 846
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
                -15
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Ser Gly Pro Val Asp
Xaa Xaa Gln Thr Leu Xaa Leu Thr Cys Thr Xaa Ser Gly Val Ser Ile
Ser Ser Ser Asp Asn Cys Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys
Gly Leu Glu Trp Ile Gly Tyr Ile Tyr His Ser Gly Gly Thr Tyr Tyr
Asn Pro Thr Leu Lys Ser Arg Val Thr Ile Ser Xaa Asp Arg Ile Arg
Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Xaa Asp Thr Ala
Val Tyr Xaa Cys Gly Arg Ala Gln Gly Arg Met Gly Ile Gly Thr Thr
                        100
                                           105
Ile Phe Asp Leu Trp Gly Gly Gly Gln Trp Ser Pro Ser Leu Gln Pro
                    115
<210> 847
<211> 140
<212> PRT
<213> Homo sapiens
<220> ·
<221> SIGNAL
<222> -19..-1
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
                -15
                                    -10
Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
```

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Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Xaa Phe
                         20
 Thr Xaa Xaa Ala Xaa His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu
 Glu Trp Met Gly Trp Ile Asn Ala Ala Xaa Gly Xaa Thr Xaa Tyr Ser
 Gln Xaa Phe Gln Xaa Arg Val Thr Xaa Thr Arg Asp Thr Ser Ala Ser
 Thr Val Ser Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
 Tyr Phe Cys Ala Arg Asp Trp Glu Ile Ala Val Val Pro Thr Ala Ile
                         100
 Asn Ser Tyr Gly Phe Asp Pro Gly Ala Arg Glu Pro
                     115
 <210> 848
 <211> 52
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -26..-1
 <400> 848
 Met Glu Ala Arg Val·Glu Arg Ala Val Gln Lys Arg Gln Val Leu Phe
                         -20
Leu Cys Val Phe Leu Gly Met Ser Trp Ala Gly Ala Glu Pro Leu Arg
                     ~5
Tyr Phe Val Ala Glu Glu Thr Glu Arg Gly Thr Xaa Leu Thr Asn Leu
            10
                                 15
Ala Lys Asp Leu
        25
<210> 849
<211> 134
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -19..-1
<400> 849
Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
                -15
                                    -10
Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Glu Val Lys Lys
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
                        20
Thr Arg Tyr Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
                    35
                                        40
Glu Trp Met Gly Trp Ile Ser Ala Xaa Asn Gly Asn Thr Asn Tyr Ala
                50
Gln Xaa Val Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Arg
Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Ile
                            85
Tyr Tyr Cys Ala Arg Glu Ile Xaa Val Xaa Xaa Cys Asp Gly Gln Leu
Gly Pro Gly Asn Leu Val
```

<210> 850 <211> 140

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 850
Met Asp Val Leu His Lys His Met Lys His Leu Trp Phe Phe Leu Leu
                         -20
                                             -15
Leu Val Ala Ala Pro Arg Trp Val Leu Ser Gln Glu Gln Leu Arg Gln
-10
Trp Gly Ala Xaa Leu Leu Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
                                 15
Ser Val Tyr Gly Gly Ser Phe Asn Gly Tyr Tyr Trp Ser Trp Ile Arg
                            30
Gln Ser Pro Gly Lys Gly Leu Glu Trp Ile Gly Gly Ile Asn His Ser
                         45
                                             50
Gly Ser Thr Leu Ser Asn Pro Ser Leu Lys Ser Arg Val Asp Leu Ser
55
                                         65
Val Asp Ala Ser Lys Asp Gln Val Ser Leu Arg Leu Lys Leu Val Thr
                                    80
                                                         85 -
Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala Arg Pro His Tyr Asp Met
Ser Thr Asp Ser Ser Phe Asp Gly Phe Asp Leu Trp
        105
                            110
<210> 851
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
Met Met Leu Leu Ala Leu Phe Phe Leu Leu Arg Ile Ala Leu Ala Ser
                   -10
                                      -5
Gln Gly Leu Leu Trp Phe His Thr Asn Phe Lys Val Phe Val Val Ser
Ile Cys Val Lys Thr Ile Ile Gly Ile Ser Gly Gly
       20
<210> 852
<211> 78
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 852
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
                                    -10
Ala Leu Ser Gln Val Gln Leu Val Gln Ser Gly Glu Val Lys Lys
Pro Gly Ala Ser Val Arg Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe
Ile Gly Tyr Tyr Val His Trp Ile Arg Gln Thr Pro Gly Arg Xaa Leu
```

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448
                                                             45
Glu Trp Met Gly Trp Val Asn Pro Xaa Thr Gly Asp Asn Gly
<210> 853
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 853
Met Phe Phe Gln Phe Trp Lys Ser Ser Ala Tyr Leu Ile Phe Val Ser
                            -30
Ile Cys Lys Gly Phe Leu Pro Val Tyr Leu Leu Leu Val Leu Ser Leu
                        -15
Ser Leu Ser Leu Cys Cys Ser Leu Leu Leu Ser Leu
                    1
<210> 854
<211> 128
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 854
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
                -15
                                    -10
Val His Ser Gln Val His Leu Val Gln Ser Gly Ala Glu Val Lys Lys
                            5.
Pro Gly Thr Pro Val Asn Ile Ser Cys Lys Ala Phe Gly Tyr Thr Phe
                        20
Pro Ala Phe Ala Ile His Trp Val Arg Gln Ala Pro Gly Gln Ser Leu
                    35
                                        40
Glu Trp Met Gly Trp Val Asn Ile Gly His Gly Asn Thr Lys Tyr Ser
                                    55
Gln Lys Phe Gln Gly Arg Leu Ala Ile Ser Arg Asp Thr Ser Ala Asn
                               . 70
Ile Val Tyr Xaa Glu Leu Ser Gly Leu Arg Ser Glu Asp Thr Ala Val
                         · 85
Tyr Tyr Cys Ala Arg Asp Asn Leu Phe Phe Gly Ser Met Gly Phe Asp
   95
                        100
                                            105
<210> 855
<211> 152
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 855
Met Ala Trp Thr Val Leu Leu Gly Leu Leu Ser His Cys Thr Gly
                       -10
Ser Val Thr Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala
```

Pro Gly Lys Thr Ala Ser Ile Thr Cys Gly Gly Asp Asn Ile Glu Ser

449 25 Gln Val Val His Trp His Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu 40 Val Ile Tyr Asp Asp Thr Asp Arg Pro Ser Gly Ile Pro Asp Arg Phe 55 Ser Gly Ser Asn Ser Gly His Thr Ala Thr Leu Thr Ile Ser Arg Val 70 75 Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Arg Ser 85 90 Ser Gly Gln Gly Ile Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Arg 100 105 Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu 120 125 Glu Leu Gln Ala Asn Lys Ala Thr 130 135 <210> 856 <211> 48 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1 <400> 856 Met Arg Leu Leu Phe Leu Leu Phe Val Cys Phe Ser Arg Gln Gly -10 -5 Leu Ala Leu Ser Leu Arg Leu Glu Cys Ser Gly Met Ile Met Ala Tyr 10 Cys Ser Ile Ser Leu Pro Gly Ser Ser Ser Pro Leu Thr Ser Ala Ser <210> 857 <211> 74 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 857 Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ser Ala Pro Arg Trp -15 -10 Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly Arg Leu Ser Leu Ala Cys Asp Val Val Glu Leu Ser Pro 20 25 Pro Ala Pro Arg Gly Gly Ser Ala Val His Leu Arg Asn Leu Ser Ser 35 . Trp Glu Pro His Leu Gln Pro Val Ser Gly 50 <210> 858 <211> 57 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -32..-1

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<400> 858
Met Thr Tyr Phe Pro Leu Gly Arg Tyr Pro Val Met Gly Leu Leu Asp
        -30
                            -25
Gln Met Val Val Phe Leu Leu Leu Leu Val Ser Thr Leu Ser Ser
                        -10
Val Val Val Leu Leu Val Cys Ile Pro Thr Ser Ser Val Lys Leu Phe
        · 5
Pro Phe His His Ile His Thr Asn Trp
<210> 859
<211> 30
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 859
Met Glu Phe Gly Leu Ser Trp Val Leu Leu Val Ala Met Leu Arg Gly
           -15
                                   -10
Leu Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Thr Ala
                          5
<210> 860
<211> 57
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 860
Met Tyr Leu Ser Leu Leu Ile Leu Leu Glu Asn Val Ser Gly Phe
                 -10
Pro Phe Pro Leu Ile Phe Gln Leu His Ala Ser Pro Gly His Lys Ile
          5
                               10
Leu Pro Asp Cys Met Ile Tyr Ser Ile Thr Val Ser Leu Met Phe Pro
        20
                           25
Val Val Asp Tyr Ile Ser Thr Gln Gly
    35
                        40
<210> 861
<211> 31
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -28..-1
<400> 861
Met Met Arg Ala Phe Tyr Leu Ala Ile Leu Phe Cys Leu Ser Leu Ser
                               -20
Leu Trp Phe Xaa Cys Leu Leu Phe Leu Leu Phe Ala Trp Pro Gly
                          - 5
<210> 862
<211> 102
<212> PRT
<213> Homo sapiens
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<220>

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<221> SIGNAL
<222> -20..-1
<400> 862
Met Ala Trp Thr Pro Leu Leu Phe Leu Thr Leu Leu Leu His Cys Thr
                   -15
                                     -10 .
Gly Ser Leu Ala Gln Leu Val Leu Thr Gln Ser Pro Ser Ala Ser Ala
Ser Leu Gly Ala Ser Val Lys Leu Thr Cys Thr Leu Ser Ser Gly His
                           20
Ser Asn Tyr Gly Ile Ala Trp Tyr Gln Gln Gln Pro Glu Lys Gly Pro
                        35
Arg Phe Leu Met Lys Val Asn Ser Asp Gly Ser His Met Lys Ala Asp
                    50
                                       55
Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Ala Glu Arg Tyr
               65
                                    70
Leu Ser Ile Ser Ser Leu
            80
<210> 863
<211> 18
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
<400> 863
Met Pro Leu Ala Leu Phe Phe Leu Leu Ser Val Ala Leu Ala Ile Gln
               -10 .
Gly Gln
<210> 864
<211> 129
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 864
Met Asp Trp Thr Trp Arg Xaa Phe Cys Leu Leu Ala Val Ala Pro Gly
               -15
                                   -10
Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
                       20
Thr Ser His Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
                   35
Glu Trp Met Gly Ile Ile Tyr Pro Asp Ser Asp Thr Thr Lys Tyr Xaa
Gln Asn Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
                               70
Thr Val Tyr Met Glu Leu Ser Ser Leu Thr Ser Asp Asp Thr Ala Val
                           85
Tyr Tyr Cys Ala Arg Glu Ala Tyr Ser Gly Ser Tyr Arg Phe Asp Tyr
                       100
Trp
110
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<210> 865
<211> 124
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 865
Met Asp Leu Met Cys Lys Lys Met Arg His Leu Trp Phe Leu Leu Leu
-25
                       -20
                                           -15
Leu Val Ala Ala Pro Arg Trp Val Leu Ser Gln Leu Gln Leu Gln Glu
                   ~ 5
Ser Gly Pro Gly Leu Val Lys Ala Ser Glu Thr Leu Ser Leu Ala Cys
           10
                              15
Ser Val Ser Gly Asp Ser Ile Ser Ser Gly Asn Tyr Tyr Trp Gly Trp
                           30
                                              35
Ile Arg Gln Pro Pro Gly Lys Gly Leu Gln Trp Leu Gly Ser Leu Trp
            45
Asn Arg Gly Gly Pro Gln Tyr Asn Xaa Ser Leu Lys Asn Arg Val Thr
         . 60
                                      65
Val Ser Val Asp Thr Ser Thr Asn His Phe Phe Leu Arg Leu Asn Ser
              . 75
                                  80
Val Asn Xaa Gly His Gly Asn Leu Leu Cys Ala
<210> 866
<211> 32
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 866
Met Arg Xaa Xaa Leu Xaa Leu Ser Val Leu Leu Gly Xaa Xaa Xaa
                   -10
                                      -5
Lys Xaa Asp Phe Val Gly His Gln Val Leu Arg Ile Ser Val Ala Asp
                                   10
<210> 867
<211> 38
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1
<400> 867
Met Ala Glu Ser Arg Glu Glu Gly Glu Ser Cys Val Glu Ser His Cys
                      -30
Val Leu Phe Phe Thr Leu Phe Phe Leu Leu Phe Phe Cys Phe Val Phe
                   -15
                                      -10
Cys Leu Arg Gly Gln Gly
<210> 868
<211> 110
<212> PRT
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453
 <213> Homo sapiens
<220>
 <221> SIGNAL
 <222> -19..-1
 <400> 868
Met Glu Leu Gly Leu Ser Trp Leu Phe Leu Val Ala Phe Leu Lys Gly
                -15
Val Gln Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln
                         5
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
Ser Ser Tyr Ala Met Leu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
                                        40
Glu Trp Val Ser Gly Ile Ser Ala Gly Ala Asp Asp Thr Tyr Asp Ala
                                    55
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Lys Lys
                                70
Ile Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Arg
<210> 869
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 869
Met Ala Val Ser Val Leu Arg Leu Thr Val Val Leu Gly Leu Leu Val
                               -15
Leu Phe Leu Thr Cys Tyr Ala Asp Asp Lys Pro Asp Lys Pro Asp Asp
Lys Pro Asp Asp Ser Gly Lys Asp Pro Lys Pro Asp Phe Pro Lys Phe
Leu Ser Leu Leu Gly Thr Glu Ile Ile Glu Asn Ala
             ` 30
<210> 870
<211> 106
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
Met Glu Arg Arg Leu Leu Gly Gly Met Ala Leu Leu Leu Gln
                -20
                                   -15
Ala Leu Pro Ser Pro Leu Ser Ala Arg Ala Glu Pro Pro Gln Asp Lys
Glu Ala Cys Val Gly Thr Asn Asn Gln Ser Tyr Ile Cys Asp Thr Gly
                       15
                                           20
His Cys Cys Gly Gln Ser Gln Cys Cys Asn Tyr Tyr Tyr Glu Leu Trp
                   30
                                       35
Trp Phe Trp Leu Val Trp Thr Ile Ile Ile Leu Ser Cys Cys
```

.50

Val Cys His His Arg Arg Ala Lys His Arg Leu Gln Ala Gln Gln Arg

```
Gln His Glu Ile Asn Leu Ile Ala Tyr Arg
<210> 871
<211> 37
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -27..-1
<400> 871
Met Val Val Ala Asp Arg Asn Arg Ala Ser Ser Ser Ser Tyr Leu Cys
 -25 -20 -15
Leu Leu Phe Ser Leu Ser Leu Phe Leu Cys His Glu Thr Val Cys
                      -5
  -10
Asp Arg Ala Thr Cys
               10
<210> 872
<211> 142
<212> PRT .
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 872
Met Asp Trp Thr Trp Arg Phe Leu Phe Val Val Ala Ala Ala Thr Gly
             -15
                      . -10
Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
    1
Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe
                     20
Ser Xaa Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
                  35
                                     40
Clu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Xaa Tyr Ala
              50
                                 55
Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Xaa Ser Thr Xaa
          65
                             70
Thr Xaa Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Xaa
      80
                                 . . .
                         85
                                           90
Tyr Tyr Cys Ala Arg Gly Gln Ala Pro Gly Arg Val Val Pro Leu
                     100
                                       105
Phe Leu Trp Gly Gln Gly Thr Trp Ser Pro Ser Pro Gln Pro
                115
<210> 873
<211> 87
<212> PRT
<213> Homo sapiens
<220> '
<221> SIGNAL
<222> -45..-1
<400> 873
Met Thr Tyr Ser Tyr Ser Phe Phe Arg Pro Glu Leu Ile Val Asn His
-45
               -40 -35
Leu Asn Tyr Val His Ser Glu Ala Asn Arg Arg Thr Lys Thr Lys Thr
```

-20

- 25

```
455
Leu Leu Ser Leu Ser Phe Leu Asp Glu Thr Ser Gly Leu Ser Thr
            -10
His Leu Pro Cys Leu Ser Leu Ser Lys Glu Cys Gly Val Leu His Leu
                        10
                                            15
Asp Ile His Gly Lys Lys Glu Asp Met Arg Asp Glu Val Leu Leu Ala
                    25
                                        30
Leu Asn Xaa Cys Thr His Arg
                40
<210> 874
<211> 79
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 874
Met Lys Ser Phe Ser Arg Ile Leu Phe Leu Val Phe Leu Leu Ala Cly
                -15
                                   -10
Leu Arg Ser Lys Ala Ala Pro Ser Ala Pro Leu Pro Leu Gly Cys Gly
Phe Pro Asp Met Ala His Pro Ser Glu Thr Ser Pro Leu Lys Gly Ala
                        20
Ser Glu Asn Ser Lys Arg Asp Arg Leu Asn Pro Glu Phe Pro Gly Thr
                   35
                                        40
Pro Tyr Pro Glu Pro Ser Lys Leu Pro His Thr Val Ser Leu Glu
           50
                                    55
<210> 875
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -41..-1
<400> 875
Met Arg Val Pro Ile Phe Pro His Pro His Gln Leu Ser Leu Leu Phe
                       -35
                                            -30
Ile His Leu Phe Ile Tyr Leu Phe Arg Glu Arg Val Ser Leu Cys His
                                        -15
                   -20
Leu Gly Trp Ser Ala Val Val Gln Ser Gln Pro Thr Thr Leu Thr
                -5
Ser Arg Ala
      10
<210> 876
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 876
Met Trp Lys Glu Ser Ser His Gly Cys Asn Asn Leu Gly Ser Ser Tyr
                                                -25
                           -30
Leu Asp Asp Thr Gly Val Gly Ser Phe Leu Phe Val Leu Phe Cys Phe
                                            -10
```

-15

-20

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Gly Gly Ser Arg Ala Leu Leu Leu Pro Gly Ser Gly
<210> 877
<211> 26.
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 877
Met His Thr Phe Leu Cys Leu Leu Phe Tyr Leu Ile Val Ser Cys Gly
                 -10
                                          - 5
Ala Val Phe Leu Thr Val Pro Ser Pro Gln
           5
1
<210> 878
<211> 52
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -39..-1
<400> 878
Met Ala Trp His Pro Thr Pro Pro Pro Leu Xaa Xaa Pro Pro Pro Leu
               -35
                            -30
Xaa Arg Xaa Ser Leu Pro Ala Cys Ala Asp Ser Ile Ile Leu Xaa Leu
                             -15
                                                  -10
          -20
Xaa Phe Pro Gly Ile Leu Gly Gln Ala His Leu Xaa Ser Glu Gln Trp
     - 5
Thr Gln Tyr Leu
10
<210> 879
<211> 37
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 879
Met Pro Ile Leu Pro Gln Asp Ile Leu His Leu Leu Ile Leu Leu Ser
                      -15
 -20
Gly Thr Cys Phe Thr Trp Ile Leu Leu Trp Leu Pro Leu Ser Pro Leu
-5
Leu Gly Leu Lys Cys
          15
<210> 880
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
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457 <400> 880 Met Lys Ala Leu Gly Ala Val Leu Leu Ala Leu Leu Leu Cys Gly Arg -15 -10 Pro Gly Arg Gly Gln Thr Gln Gln Glu Glu Glu Glu Asp Glu Asp 1 His Gly Pro Asp Asp Tyr Asp Glu Glu Asp Glu Asp Glu Val Glu Glu 20 Glu Glu Thr Asn Arg Leu Pro Gly Gly Arg Ser Arg Val Leu Leu Arg 35 Cys Tyr Thr Xaa Xaa Ser Leu Pro Arg Asp Glu Arg Cys Asn Leu Thr 50 Gln Asn Cys Ser His <210> 881 <211> 88 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1 <400> 881 Met Lys Glu Tyr Val Leu Leu Phe Leu Ala Leu Cys Ser Ala Lys -10 - 5 Pro Phe Phe Ser Pro Ser His Ile Ala Leu Lys Asn Met Met Leu Lys 5 10 25 Asp Asp Glu Asp Asn Ser Leu Phe Pro Thr Arg Glu Pro Arg Ser His 40 45 Phe Phe Pro Phe Asp Leu Phe Pro Met Cys Pro Phe Gly Cys Gln Cys 55. Tyr Ser Arg Val Val His Cys Ser 70 <210> 882 <211> 95 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 882 Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp Ala Met Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Arg Leu Val Lys Pro Ser Gly Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Met Ala Thr Ser Asp Trp Trp Ser Trp Phe Arg Gln Thr Pro Glu Lys Gly 35 Leu Glu Trp Ile Gly Glu Ile Phe Gln Thr Gly Pro Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Ser Met Ser Val Asp Met Ser Lys

<210> 883

<sup>&</sup>lt;211> 129

<sup>&</sup>lt;212> PRT

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458
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 883
Met Asp Leu Thr Cys Lys Met Lys His Leu Trp Phe Phe Leu Leu
   -25
                        -20
                                            -15
Leu Val Ala Ala Pro Arg Trp Ala Leu Ser Gln Leu Gln Leu Gln Glu
                    -5
Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
            10
                                15
Thr Val Ser Gly Glu Ser Ile Thr Thr Asn Ser Phe Cys Trp Ala Trp
                            30
Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu Gly Thr Val Cys
   40
                        45
Tyr Gly Gly Thr Thr Tyr Xaa Asn Xaa Ser Leu Lys Ser Arg Val Lys
55
                    60
                                        65
Leu Ser Leu Asp Thr Ser Thr Asn Gln Phe Ser Leu Lys Val Thr Ser
               75
Met Thr Ala Gly Asp Ala Ala Val His Tyr Cys Ala Gly Leu Arg Val
                                95
                                                    100
Ser
<210> 884
<211> 66
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -63..-1
<400> 884
Met Ala Asn Gly Thr Asn Ala Ser Ala Pro Tyr Tyr Ser Tyr Glu Tyr
           -60
                               -55
                                                    -50
Tyr Leu Asp Tyr Leu Asp Leu Ile Pro Val Asp Glu Lys Lys Leu Lys
      -45
                           -40
                                                -35
Ala His Lys His Ser Ile Val Ile Ala Phe Trp Val Ser Leu Ala Ala
                       -25
                                           -20
Phe Val Val Leu Leu Phe Leu Ile Leu Leu Tyr Met Ser Trp Ser Ala
-15
                -10
                                        -5
Ser Pro
<210> 885
<211> 133
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 885
Met Asp Trp Thr Trp Arg Phe Leu Phe Val Val Ala Ala Ala Thr Gly
               -15
                                   -10
Val Gln Ser Gln Xaa Xaa Leu Xaa Gln Ser Gly Ala Glu Val Lys Lys
Pro Gly Ser Ser Val Lys Val Ser Cys Xaa Ala Ser Gly Gly Ile Xaa
                       20
                                            25
```

Ser Xaa Tyr Ser Phe Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Phe

35

<222> -19..-1

```
Glu Trp Leu Gly Arg Ile Ile Pro Ile Leu Gly Ile Thr Asn Tyr Ala
Glu Lys Phe Arg Gly Arg Leu Thr Ile Thr Val Asp Lys Ser Thr Arg
                                70
Val Val Tyr Met Glu Gln Ser Ser Leu Thr Ser Ala Asp Thr Ala Val
                           85
Tyr Tyr Cys Ala Lys Pro Thr Met Thr Ser Glu Leu Arg Val Tyr Tyr
                        100
                                            105
Gln Xaa Thr Leu Trp
110
<210> 886
<211> 30
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1
<400> 886
Met Trp Asn Arg Tyr Phe Val Phe Tyr Leu Leu Leu Ser Ala Phe
      -20
                           -15
Thr Ser Gln Thr Val Ser Gly Gln Arg Lys Lys Gly Pro Arg
<210> 887
<211> 142
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 887
Met Lys His Leu Gly Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
                                    -10
               -15
Val Leu Ser Gln Leu Gln Leu Gln Glu Ser Gly Ser Gly Leu Glu Lys
Pro Ser Gln Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile
Ser Ser Asp Asp Leu Ser Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys
                    35
Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Gln Asn Glu Arg Thr Leu Tyr
                                    55
Asn Pro Ser Leu Lys Ser Arg Ala Ala Ile Ser Val Asp Arg Ser Lys
Asn Gln Phe Ser Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Met Ala
                            85
Val Tyr Tyr Cys Ala Thr Ser Val Met Xaa Ser Phe Gly Gly Val Leu
                        100
Val Pro Asn Leu Phe Leu Thr Thr Gly Ala Arg Glu Ser Arg
                    115
<210> 888
<211> 155
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<400> 888
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Gly Pro Arg Trp
                                    -10
               -15
Val Leu Ser Gln Val Gln Leu Xaa Glu Ser Gly Pro Arg Leu Val Lys
Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ala Ser Val
                        20
Ser Ser Arg Gly Tyr Tyr Trp Thr Trp Ile Arg Gln Leu Pro Gly Lys
                    35
Gly Leu Glu Trp Ile Gly Tyr Ile Xaa Tyr Thr Gly Ser Thr Phe Tyr
                50
                                    55
Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Ile Asp Thr Ser Lys
                                70
Asn Gln Phe Ser Leu Asn Leu Arg Ser Val Thr Thr Ala Asp Thr Ala
                           85
Val Tyr Tyr Cys Ala Arg Asp His Phe Asp Leu Leu Phe Asp Pro Trp
                       100
                                           105
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
                                       120
                   115
Ser Val Phe Pro Leu Ala Xaa Ser Ser Lys Ser
               130
<210> 889
<211> 63
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -41..-1
<400> 889
Met Ala Cys Arg Glu Arg Pro Arg Pro Leu Leu Trp Arg Ser Arg Gly
                        -35
                                         -30
Arg Phe Phe Asn Trp Gly Lys Leu Phe Phe Cys Phe Val Leu Xaa Leu
                                        -15
                    -20
Phe Cys Phe Val Phe Glu Ala Glu Ser Arg Ser Val Ala Gln Ala Gly
                -5
Val Gln Trp Arg Tyr Phe Gly Ser Leu Gln Ala Leu Pro Pro Trp
<210> 890
<211> 25
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 890
Met His Glu Phe Ile Ser Gly Phe Phe Ile Leu Phe His Trp Ser Leu
                        -15
Cys Leu Cys Leu Cys Gln Tyr His Ala
                    1
<210> 891
<211> 44
<212> PRT
<213> Homo sapiens
<220>
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<221> SIGNAL

<222> -42..-1

<400> 891

Met Ala Tyr Ala Ile Ser Pro Phe His Ser Ser Trp Asn Pro Leu Phe
-40 -35 -30

Thr Ser His Lys Ala Ser Ala Ser His Ser His Leu Gly Leu Leu Val

Cys Leu Phe Ala Val Thr Ser Ile Leu Cys Ser Ser -10 -5 1

<210> 892

<211> 60

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -15..-1

<400> 892

Met Ser Pro Val Leu Leu Leu Ala Leu Leu Gly Phe Ile Leu Pro Leu -15 -5 1

Pro Gly Ser Ala Xaa Ala Xaa Ser Ala Ser Leu Gly Gln Phe Ser Met 5 10 15

Cys Gly Arg Cys Pro Thr Cys Pro Gly Asn Gly Pro Leu Arg Thr Pro 20 25 30

Ala Ala Thr Xaa Xaa Xaa Val Pro Gly His Val Asp 35 40 45

<210> 893

<211> 154

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -23..-1

<400> 893

Met Ala Thr Ala Met Asp Trp Leu Pro Trp Ser Leu Leu Phe Ser
-20 -15 -10

Leu Met Cys Glu Thr Ser Ala Phe Tyr Val Pro Gly Val Ala Pro Ile
-5 5

Asn Phe His Gln Asn Asp Pro Val Glu Ile Lys Ala Val Lys Leu Thr 10 15 20 25

Ser Ser Arg Thr Gln Leu Pro Tyr Glu Tyr Tyr Ser Leu Pro Phe Cys 30 35 40

Gln Pro Ser Lys Ile Thr Tyr Lys Ala Glu Asn Leu Gly Glu Val Leu
45 50 55

Arg Gly Asp Arg Ile Val Asn Thr Pro Phe Gln Val Leu Met Asn Ser 60 65 70

Glu Lys Cys Glu Val Leu Cys Ser Gln Ser Asn Lys Pro Val Thr

Leu Thr Val Glu Gln Ser Arg Leu Val Ala Glu Arg Ile Thr Glu Asp 90 95 100 105

Tyr Tyr Val His Leu Ile Ala Asp Asn Leu Pro Val Ala Thr Gly Trp
110 115 120

Ser Ser Thr Pro Thr Glu Thr Ala Met Thr 125 130

<210> 894

<222> -17..-1

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 894
Met Pro Ser Pro Cys Leu Ile Ser Leu Leu Gln Cys Ala His Val Ser
            -15
                                -10
Leu Gly Leu Gln Tyr Pro Cys Xaa Leu Leu Pro
                        5
<210> 895
<211> 53
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 895
Met Asn Leu Ser Leu Val Leu Ala Ala Phe Cys Leu Gly Ile Ala Ser
                           -10
       -15
                                                -5
Ala Val Pro Lys Phe Asp Gln Asn Leu Asp Thr Lys Trp Tyr Gln Trp
                                        10
Lys Ala Thr His Arg Arg Leu Tyr Gly Ala Asn Glu Glu Gly Trp Arg
                20
                                   25
Arg Ala Ala Trp Glu
            35
<210> 896
<211> 85
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 896
Met Glu Phe Gly Leu Asn Trp Val Phe Leu Val Ala Ile Phe Thr Gly
                -15
                                    -10
Val His Cys Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln
Pro Gly Arg Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe
                        20
Gly Asp Tyr Ala Met Thr Trp Phe Arg Gln Ala Ser Gly Lys Arg Leu
                    35
                                        40
Glu Trp Leu Gly Phe Ile Arg Asn Arg Gly Ser Gly Gly Ser Ala Glu
                50
                                    55
Tyr Gly Ala Ser Val
<210> 897
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<400> 897
 Met Lys Asn Cys Leu Leu Ile Leu Leu Met Leu Leu Leu Phe Ala Ile
                            -10
                                         . -5
 His Ile Asn Arg Met Asn Val Arg Asn Val Gly Asn Thr Leu Val Val
  1.
                                         10
 Val Gln Ile Leu Phe Ser Ile Arg Val Phe Ile Leu Glu Arg Asn Pro
                20
                                     25
 Leu Asn Val
 <210> 898
 <211> 149
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -19..-1
 <400> 898
 Met Glu Leu Gly Leu Ser Trp Ile Phe Leu Leu Ala Ile Leu Lys Gly
                -15
                                    -10
 Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Leu Val Gln
 Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
Asp Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
                    35
                                        40
Glu Trp Val Ser Gly Ile Thr Trp Asn Ser Gly Xaa Ile Gly Tyr Ala
                50
                                    55
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                                70
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Thr Glu Asp Thr Ala Phe
                            85
Tyr Phe Cys Ala Lys Ala Arg Gly Leu Phe Ser Asp Thr Trp Pro Tyr
                       100
                                            105
Xaa His Tyr Ala Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val
                   . 115
                                        120
Ser Ser Ala Ser Thr
                130
<210> 899
<211> 25
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
Met Leu Leu Val Phe Phe Val Leu Trp Thr Cys Ser Leu Ala Leu Leu
               -10
Ala Ser Ser Pro Ile Ala Ala Xaa Pro
       5
<210> 900
<211> 127
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<222> -19..-1

<400> 900 Met Asp Trp Thr Trp Arg Ile Leu Leu Leu Val Ala Ala Ala Thr Asp -15 -10 Ala Ser Ser Gln Met Gln Leu Leu Gln Ser Gly Pro Glu Val Lys Lys Thr Gly Ser Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Asp Thr Leu 20 Ala Tyr His Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Ala Leu 35 40 Glu Trp Met Gly Trp Ile Thr Pro Phe Ser Gly Asp Thr Asn Phe Ala 50 55 Gln Arg Phe Gln Asp Arg Leu Thr Phe Thr Arg Asp Arg Ser Met Ser 65 70 Thr Val Tyr Met Thr Leu Thr Ser Leu Ile Ser Glu Asp Thr Ala Met 80 85 Tyr Tyr Cys Ala Thr Asp Gly Arg Arg Thr Asn Arg Leu Phe Glu 100 <210> 901 <211> 68 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1 <400> 901 Met Ala Gly Gln Leu Leu Gly Cys Leu Leu Trp Leu Leu Thr His Ile -10 -15 Lys Ala Gln Asp Ser Val Arg Asp Ala Tyr Trp Lys Thr Gly Ser Cys 10 Pro Pro Pro Phe Leu His Val Ser Thr Phe Xaa Xaa Lys Leu Thr Phe 20 25 , Ser Thr Lys Gly Asn Leu Leu His Ser Ile Pro Leu Ser Ser Pro Leu Ala Cys Val Leu <210> 902 <211> 105 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -91..-1 <400> 902 Met Lys Glu Ala Val Pro Pro Gly Cys Thr Lys Ser Pro Ser His Phe -85 Ser Glu Gly Phe Asp Arg Trp Ala Leu Glu Glu Thr Pro Pro Glu Asn -70 -65 Leu Ile Gly Ala Leu Leu Ala Ile Phe Gly His Leu Val Val Ser Ile

Ala Leu Asn Leu Gln Lys Tyr Cys His Ile Arg Leu Ala Gly Ser Lys
-40

Asp Pro Arg Ala Tyr Phe Lys Thr Lys Thr Trp Trp Leu Gly Leu Phe
-25

Leu Met Leu Leu Gly Glu Leu Gly Val Phe Ala Ser Tyr Ala Phe Ala
-10

-55

-60

-45

-45

Asp Leu Ala Gly Ser Lys
-30

-30

-15

Leu Met Leu Leu Gly Glu Leu Gly Val Phe Ala Ser Tyr Ala Phe Ala
-10

-5

<210> 906 <211> 23

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465
 Pro Leu Ser Leu Ile Val Pro Leu Ser
                 10
 <210> 903
 <211> 44
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -18..-1
 <400> 903
 Met Ala Phe Leu Trp Leu Leu Ser Cys Trp Ala Leu Leu Gly Thr Thr
                                 -10
                                                     -5
 Phe Gly Cys Gly Val Pro Ala Ile His Pro Gly Cys Gln Leu Ser Pro
       1
                       5 -
                                             10
 Arg Leu Pro Pro Thr Leu Leu Pro Thr Glu Arg Gly
                     20
 <210> 904
 <211> 82
 <212> PRT
 <213> Homo sapiens
 <220>
<221> SIGNAL
 <222> -20..-1
 <400> 904
 Met Ala Pro Phe Gln Asn Phe Leu Trp Leu Phe Phe Val Leu Asn Leu
                    -15
                                    -10
 Gly Ser Phe Ala Phe Ser Ser Xaa Pro Asn Ser Leu Phe Tyr Thr Ile
                                5
                                                    10
 His Phe Gly Pro Asn Phe Phe Thr Leu Leu Tyr Lys Gln Gly Ala Glu
                            20
 Met Cys Val Tyr Val Phe Asn Phe Leu Tyr Pro Phe Ala Leu Gly Tyr
                        35
                                            40
 Phe Phe Ser Tyr Asp Ile Leu Asp Leu Pro Val Xaa Val Arg Pro Pro
 45
                   50
                                        55
. Ser Gly
<210> 905
 <211> 54
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -35..-1
<400> 905
Met Asp Phe Thr Gln Cys His Ser Leu Leu Leu Arg Val Glu Tyr Ser
                -30
                                        -25
Pro Val Ser Val Cys Phe Leu Leu Leu Ser Val Ala Phe Asn Gln Leu
                -15
                                    -10
Val Phe Ala Leu Tyr Pro Ile Gln Ala Thr Xaa Cys Phe Ser Xaa Val
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Ser Leu Pro Phe Pro Ala
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<221> SIGNAL <222> -44..-1

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<212> PRT
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 Met Leu Leu Leu Leu Ala Cys Gly Val Pro Ser Leu Trp Pro Phe
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                    -10
 Ala Leu Ala Leu Leu Lys Thr
 <210> 907
 <211> 43
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 <222> -23..-1
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 Met Phe Ile Glu Asn Ile Gly Leu Lys Phe Ser Phe Leu Leu Leu His
          - -20
                               -15
                                                   -10
 Leu Cys Gln Val Leu Leu Ser Arg Arg Ala Gly Thr Ile Pro Thr Glu
  -5
                           1
 Thr Ile Pro Lys Lys Leu Arg Arg Arg Asp Gly
<210> 908
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Met Gln Asn Arg Thr Gly Leu Ile Leu Cys Ala Xaa Ala Leu Leu Met
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                                   -15
Gly Phe Leu Met Val Cys Leu Gly Ala Phe Phe Ile Ser Trp Gly Ser
Ile Phe Asp Cys Gln Gly Ser Leu Ile Ala Ala Tyr Leu Leu Leu Pro
                       15
Leu Gly Phe Val Ile Leu Leu Ser Gly Ile Phe Trp Ser Asn Tyr Arg
                   30
                                       35
Gln Val Thr Glu Ser Lys Gly Val Leu Arg His Met Leu Arg Gln His
               45
                                   50
Leu Ala His Gly Ala Leu Pro Val Ala Thr Val Asp Ser Ala Ala Leu
Leu Lys Ile Met Cys Lys Gln Leu Leu
<210> 909
<211> 52
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Met Lys Val Glu Gly Glu Lys Leu Tyr Arg Leu Leu Arg Ser Gly
                -40
                                    -35
Asp Leu Phe Lys Phe His Gln Pro His Phe Tyr Glu Leu Ser Gly Leu
          -25
                                -20
                                                    -15
Thr Cys Thr Ser Ser Leu Leu Ser Phe Ala Leu Gly Arg Ser Ile Pro
     -10
                            -5
Gly Ser Phe Pro
5.
<210> 910
<211> 60
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<222> -19..-1
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Met Glu Ser Arg Thr Leu Leu Leu Phe Ser Gly Ala Val Ala Leu
                                    -10
                ~15
Ile Gln Thr Trp Ala Gly Glu Cys Gly Val Gly Arg Glu Lys Ala Ser
Ala Gly Arg Ser Glu Gly Pro Ala Arg Arg Ser Lys Ser Ala His Ile
                        20
Xaa Asn Tyr Arg Leu Gln Leu Gln Ser Arg Gln Gly
                   35
<210> 911
<211> 35
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<213> Homo sapiens
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<222> -16..-1
<400> 911
Met Ser Asn Ser Val Pro Leu Leu Cys Phe Trp Ser Leu Cys Tyr Cys
                       -10
Phe Ala Ala Gly Ser Pro Val Pro Phe Gly Pro Glu Gly Arg Leu Glu
                                    10
Asp Lys Leu
<210> 912
<211> 52
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -14..-1
<400> 912
Met Pro Trp Thr Ile Leu Leu Phe Ala Ala Gly Ser Leu Ala Ile Pro
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Ala Pro Ser Ile Arg Val Val Pro Pro Tyr Pro Ser Ser Gln Glu Asp
Pro Ile His Ile Ala Cys Met Ala Ala Gly Asn Phe Pro Gly Ala Asn
Phe Thr Leu Tyr
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WO 99/53051
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Met Ala Glu Gly Glu Arg Val Cys Ala Ser Val Val Pro Ser Ala Leu
                -60
                                    -55
Arg Thr Leu Lys Arg Arg Ser Asn Leu Ser Arg Ile Pro Ala Gly Gln
                                 -40
                                                    -35
Glu Lys Glu Gly Lys Ser Arg His Val Ala Pro Pro Phe Arg Phe Phe
        -30
                            -25
                                                 -20
Pro Phe Ser Gly Phe Leu Phe Phe Gly Phe Leu Phe Pro Val Phe Ser
                        -10
Phe Pro Ser
<210> 914
<211> 71
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<222> -13..-1
<400> 914
Met Phe Cys Leu Ala Ala Ile Leu Ala Ser Ala Ser Ala Gln Arg Phe
            -10
                               - 5
Pro Ser Ala Phe Ser Pro Ser Pro Phe Xaa Trp Leu Xaa Gln Cys Xaa
                       10
Thr Ala Thr Ser Leu Gly Phe Xaa Thr Val Cys Xaa Asn Ser Ile Ile
                    25
                                       30
Ser Leu Trp Tyr Leu Xaa Gly Val Pro Pro Glu Val Xaa Glu Leu Pro
                40
                                    45
Phe Phe Pro Tyr Cys Ser Met
            55
<210> 915
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<400> 915
Met Val Asp Gly Thr Leu Leu Leu Leu Ser Glu Ala Leu Ala Leu
       -15
                           -10
Thr Gln Thr Trp Ala Gly Ser His Ser Xaa Lys Tyr Phe His Thr Ser
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5.0
 Tyr Tyr Asn Gln Ser Glu Ala Gly Ser Xaa Thr Leu Gln
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 <400> 916
 Met Asn Phe Arg Gly Pro Gln Thr Phe Ser Leu Ser His Ser Leu Val
        -25
                            -20
                                                 -15
 Leu Ser Leu Ile Ser Leu Ser Ile Ala Trp Ser Met Val Glu Met Xaa
  -10
                                             1
 Thr Ser Ala Ser Tyr Lys Gln Lys Phe Ala Leu Arg Ile Leu Val Val
                10
                                     15
Gln Leu Pro Thr Trp Val Glu Cys Pro Val Asn His Arg Cys Ala Leu
                                 30
 Gly Arg Lys Asn Cys Ser Ile Arg Thr Gln Pro
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Met Thr Gly Ile Ser Ile Cys Ser Cys Ile Cys Leu Phe Leu Pro Ser
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Leu Ile His Ser Phe Pro Pro Cys
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Met Asp Leu Leu Cys Lys Asn Met Lys His Leu Trp Phe Phe Leu Leu
                       -20
Leu Val Ala Ala Pro Arg Trp Val Gln Leu Gln Glu Ser Gly Pro Arg
                   - 5
Leu Val Arg Pro Pro Glu Thr Leu Lys Pro Ser Glu Thr Leu Ser Leu
           10
                               15
Thr Cys Thr Ile Ser Gly Asp Ser Met Ser Ser Ala Ser Tyr Tyr Trp
                           30
Ala Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Phe Ile Gly Arg
                                           50
Ala Leu Tyr Ser Gly Thr Thr Asp Tyr Asn Pro Ser Leu Ser Ser Arg
55
                   60
Ile Thr
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<211> 52
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<213> Homo sapiens
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<222> -45..-1
<400> 919
Met Ser Ser Glu Lys Ser Gly Leu Pro Asp Ser Val Pro His Thr Ser
                   -40
                                     -35
Pro Pro Pro Tyr Asn Ala Pro Gln Pro Pro Ala Glu Pro Pro Ala Pro
                        -20
             -25
Pro Leu Ser Leu Cys Leu Ser Leu Cys His Thr His Thr His
            -10
                               - 5
Thr His Thr His
 5
<210> 920
<211> 46
<212> PRT
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<222> -28..-1
<400> 920
Met Thr Pro Ala Leu Arg Cys Ala Phe Ala Leu Ala Ile Ala Gly Leu
         ~25
                               -20
                                                  -15
Val Ser Leu Leu Met Gln Pro Glu Gly Ala Leu Gly Glu Glu Ala Ala
 -10
                           -5
Ser Ala Ala Ala Gln Gly Arg Gln Leu Ala Glu Leu Arg Leu
                  10
<210> 921
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<400> 921
Met Ser Gly Leu Phe Pro Val Pro Val Arg Val Asn Val Asp Ile Ala
           -35
                           . -30
Gln Asn Ile Thr Cys Ser Ser Phe Ser Leu Leu Leu Ile Phe Leu Ser
     -20
                           -15
                                              -10
Phe Pro Tyr Thr Leu Cys Ile Leu Tyr Arg Val Lys Ser Tyr Thr Pro
                      1
Thr Glu Ser Ile Thr Ala Phe Asn Leu Thr Ile Gly Xaa Phe Pro Tyr
              15
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Leu Xaa Xaa Ser Thr Pro
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  <222> -33..-1
  <400> 922
  Met Cys Arg Ala Ala Cys Ile Ile Arg Met Ala Val Arg Ile Ser Phe
             -30
                                 -25
  Phe Leu Ser Tyr His Ala Leu Ser Leu Cys Leu Cys Thr Cys Ala Phe
    -15
                             -10
                                         - 5
  Ala Phe Leu Ser Leu Leu Gly
     1
                     5
  <210> 923
  <211> 59
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -17..-1
  <400> 923
  Met Lys Phe Leu Leu Leu Xaa Ala Leu Gly Phe Leu Xaa Gln Val Asn
         -15
                           -10
                                                 - 5
  Pro Xaa Pro Ile Xaa Gly Gly Ser Lys Met Cys Glu Xaa His Pro Arg
                                        10
  Ile Leu Gln Asp Met Leu Pro Leu Gly Gly Asp Ser Ile Val His Val
                 20
                                     25
 Gln Arg Xaa Gln Lys Met Leu His Gln Leu Leu
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 Met Val Pro Trp Val Arg Thr Met Gly Gln Lys Leu Lys Gln Arg Leu
                             -35
                                                ~30
 Arg Leu Asp Val Gly Arg Glu Ile Cys Arg Gln Tyr Pro Leu Phe Cys
                        -20
                                             -15
 Phe Leu Leu Cys Leu Ser Ala Ala Ser Leu Leu Leu Asn Arg Tyr
                    -5
 Ile His Ile Leu Met Ile Phe Trp Ser Phe Val Ala Gly Val Val Thr
                                15
 Phe Tyr Cys Ser Leu Gly Pro Asp Ser Leu Leu Pro Asn Ile Phe Phe
                            30
 Thr Ile Lys Tyr Lys Pro Lys Gln Leu Gly Leu Gln Glu Leu Phe Pro
                        45
 Gln Gly His Ser Cys Ala Val Cys Gly
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Met Ala Trp Gly Ser Pro Gly Lys Ile Phe Leu Met Gly Phe Leu Gly
                                 -25
Gly Glu Leu Val Phe Leu Leu Cys Leu Phe Xaa Leu Phe Phe Phe Ser
                              -10
Phe Leu Lys Arg Ser Phe Ala Leu Glu Cys Asn
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<221> SIGNAL
<222> -16..-1
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Met Phe Phe Ser Ile Leu Leu Leu Leu Ala Pro Pro Leu Pro Ser Ala
                      -10
                             -5
Val Ser Leu Leu Pro Phe Phe Phe Tyr Cys Val Gln
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<400> 927
Met Val Asp Phe Ile Leu Arg Ser Leu Leu Leu Val Cys Ser Trp Leu
-20
             -15
                               -10
Ser Ile Ser Leu His Ala His Thr Thr Ala Phe Cys Thr Tyr Ser Lys
 -5
               . 1
Lys Ile His Thr Val Met Ser Phe Phe Cys
             - 15
<210> 928
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<222> -16..-1
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Met Arg Ser Leu Leu Tyr Phe Leu Cys Val Ser Ser Tyr Val Thr Ser
 -15
               -10
                                        - 5
Phe Phe Phe Phe Phe Phe Phe Phe
              5
<210> 929
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Met Pro Phe Ile Ser Phe Leu Cys Leu Ile Ala Leu Ala Gly Thr Ser
                    -10
                                        - 5
Ser Thr Met Leu Arg Ser Ala Leu Ala Gly Thr Ser Ser Thr Met Xaa
                                10
Xaa Arg Ser Gly Xaa Ser Gly Xaa Pro Xaa Leu Val Xaa Val Leu Arg
                            25
Gly Asn Ala Phe Ser Phe Phe Pro Phe Ser Leu Met Xaa Ala Met Gly
  35
                        40
Cys His Arg Trp
50
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Met Tyr Thr Phe Leu Leu Gly Ala Ile Phe Ile Ala Leu Ser Ser
  -15
Arg Ile Leu Leu Val Lys
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<222> -42..-1
<400> 931
Met Cys Leu Cys Pro Cys Trp Asp Val Phe Thr Val Phe Val Cys Val
                      -35
Ser Val Cys Val Ser Val Ser Val Pro Val Gly Met Tyr Leu Val Cys
                       -20
Val Cys Val Cys Val Cys Xaa Cys Xaa Arg
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<211> 50
<212> PRT
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<222> -34..-1
<400> 932
Met Leu Ile Ala Lys Gln Ala Gln Pro Gln Gly Leu Thr Ala Ile Cys
               -30
                                   -25
                                                       -20
Phe Pro Leu Thr Pro Leu Phe Ser Leu Leu Met Leu Thr Gln Ser Pro
                               -10
                                                   - 5
Leu Ala Gly Gln Glu Gly Arg Glu Gly Gly Lys Glu Arg Tyr Leu Leu
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Val Ile
  15
  <210> 933
 <211> 62
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 Met Leu Arg Thr Trp Ser Ser Leu Pro Trp Thr Arg Phe Arg Val Cys
     -25.
                        -20
                                             -15
 Leu Leu Ser Leu Ser Leu Phe Leu Trp Ala Asn Arg Leu Glu Asp Ser
                 - 5
 Arg Ser Cys Gln Pro Asn Pro Met Ser Leu Thr Thr Leu Pro Gly His
           10
                                15
 Arg Leu Lys Glu Ala Val Trp Leu Pro Ala Pro Ser Leu Gly
    . 25
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<400> 934
Met Ala Pro Phe Leu Arg Gln Val Asp Xaa Trp Gly Ala Gln Ala Gly
                -25
                                    -20
Leu Val Val Xaa Trp Leu Leu Pro Xaa Gln Cys Ser Cys Glu Arg Ser
     -10
                                -5
Glu Gln Tyr Leu Ser Thr Cys Leu Pro Gln His Ser Ser Ile Lys Gln
                        10
                                           15
Ser Cys Ile Lys His Pro Ala Gly Pro Ile Pro Ala Gly His Leu Gln
                                       .30
Gly Lys Ala Thr Ala Ala Pro Leu
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<210> 935
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<400> 935
Met Glu Phe Gly Leu Lys Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
               -15
                                    -10
Val Arg Cys Glu Val Lys Leu Val Glu Ser Gly Gly Leu Val Gln
Pro Gly Gly Ser Leu Arg Leu Ser Cys Val Gly Ser Gly Phe Val Phe
                                           25
Asp Lys Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
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Gln Trp Val Ala Gly Ile Gly Gly Gly 50

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Met Ala Leu Ala Met Leu Val Leu Val Val Ser Pro Trp Ser Ala Ala
                        -10
Arg Gly Val Leu Arg Asn Tyr Trp Glu Arg Leu Leu Arg Lys Leu Pro
Gln Ser Arg Pro Gly Phe Pro Ser Pro Pro Trp Gly Pro Ala Leu Ala
            20
Val Gln Gly Pro Ala Met Phe Thr Glu Pro Ala Asn Asp Thr Ser Gly
                            40
Ser Lys Glu Asn Ser Ser Leu Leu Asp Ser Ile Phe Trp Met Ala Ala
                        55
Pro Lys Asn Arg Arg Thr Ile Glu Val Asn Arg Cys Arg Arg Asn
                    70
Pro Gln Lys Leu Ile Lys Val Lys Asn Asn Ile Asp Val Cys Pro Glu
               85
                                   90
Cys Gly His Leu Lys Gln Lys Xaa Val Leu Cys Ala Thr Ala Met Lys
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Met Phe Phe Tyr Ser His Phe Leu Leu Phe Pro Leu Ser Leu Leu
                -15
                             -10
Phe Thr Leu Gly Phe Leu Phe Val Phe Phe Phe Phe Phe
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Met Lys Gln Ser Lys Arg Xaa Met Val Lys Arg Arg Arg Ser Pro Ala
                       -40
                                           -35
Leu Gly Glu Glu Arg Phe Ser Pro Ser Ser Ile Leu His Pro Arg Leu
                   -25
                                       -20
Pro Leu Val Leu Leu Gly Thr Arg Val Pro Leu Ser Gly Gly Pro
               -10
                                   -5
Gly Glu Pro Asp Gln Gly Arg Ser Ala Pro Ser Trp Lys Ser Leu Ala
                          10
                                               15
Ser Thr His Xaa His Ser Arg Pro Ala Ala Gly Ala Thr Pro Ala Arg
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Pro Ala Thr Gln Ser Gln Leu Gly Pro Phe Ala Pro Pro Leu Pro Gly
                                         45 ·
 Val Arq Pro Ala Pro
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Met Leu Leu Glu Ser Leu Cys Val Leu Ser Leu Leu Val Ser Phe Lys
           -15
                                -10
Ser Ala Cys Leu Thr Arg Glu Pro Ala Phe Asp Ser Gln Ala Arg Pro
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Met Val Phe Gly Tyr Trp Lys Gln Pro Leu Ile Thr Leu Ala Lys Lys
                                             -35
Ser Val Lys Cys Ala Arg Glu Cys Leu Arg Cys Ser Leu Arg Pro Leu
                    -25
                                         -20
Val Leu Leu Tyr Leu Ser Phe Ala Ala Leu Gly Val Val Ala Leu Arg
                -10
Ser Val Glu Ser Pro Leu Ala Glu Thr His Ser Cys Trp Leu Ser Leu
                            10
Gly Met Cys Val Leu Gln Cys Glu Gln Gln Trp Val Pro Thr Pro Val
                        25
Ser Phe Leu Cys Gly Leu Ser Gly Ser Ser Thr Ile Ile Val
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<210> 941
<211> 66
<212> PRT
<213> Homo sapiens
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<222> -24..-1
<400> 941
Met Cys Val Val Cys Ser Val His Gly Val Cys Cys Val Tyr Val Val
               -20
                                    -15
Cys Leu Val Ser Cys Val Leu Cys Val Val Cys Pro Val Cys Trp Val
Met Cys Cys Val Trp Cys Ile Cys Val Cys Val Trp Cys Val Cys Cys
                                            20
Met Cys Cys Val Leu Ser Cys Val Val Ser His Gly Leu Cys Gly Val
Ser Trp
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 <213> Homo sapiens
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Met Glu Leu Gly Leu Ser Trp Val Phe Leu Val Ala Val Leu Glu Val
               -15
                        -10
Val Gln Cys Glu Ile Gln Leu Ile Asp Ala Gly Gly His Val Gln
                       5 .
           1
                                             10 -
Ala Gly Gly Ser Leu Arg Leu Ser Cys Val Ala Ser Asp Phe Leu Phe
  15
                      20
Arg Ser Tyr Trp Met Thr Trp Val Arg His Pro
                   35
<210> 943
<211> 41
<212> PRT
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<221> SIGNAL
<222> -39..-1
<400> 943
Met Ser Ile Leu Leu Arg Val Leu Gly Ile Lys Gly Cys Trp Ile Leu
               -35
                                  -30
Ser Asn Pro Phe Ser Ala Cys Ile Glu Met Ile Leu Leu Phe Leu Phe
        -20
                              -15
Leu Ile Leu Phe Ile Trp His Ile Arg
<210> 944
<211> 27
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -25..-1
<400> 944
Met Ala Glu Lys Ala Gly Ser Thr Phe Ser His Leu Leu Val Pro Ile
-25 -20
                               -15
Leu Leu Leu Ile Gly Trp Ile Val Gly Cys Thr
<210> 945
<211> 34
<212> PRT
<213> Homo sapiens
<221> SIGNAL
<222> -19..-1
Met Ala Glu Ser Arg Gly Arg Leu Tyr Leu Trp Met Cys Leu Ala Ala
                                 -10
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WO 99/53051 478 Ala Leu Ala Ser Phe Leu Met Gly Phe Met Val Gly Trp Phe Ile Lys 10 Pro Leu 15 <210> 946 <211> 40 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1 <400> 946 Met Leu Thr Ser Leu Pro Phe Leu Leu Pro Thr Ile Ser Phe Leu Leu -20 -15 Leu Leu Tyr Phe Phe Xaa Ile Ala Val Thr His Pro Ser Val Leu Ile - 5 Asn Phe Ser Phe Ser Phe Pro Arg 10 <210> 947 <211> 36 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -20..-1 <400> 947 Met Arg Lys Asp Val Arg Phe Leu Leu Phe Phe Thr Cys Gly Leu Pro -15 -10 Ala Leu His Gly Asp Ser Arg Val Glu Cys Ser Lys Ala His Pro Pro 10 Ala Met Tyr Tyr 15 <210> 948 <211> 48 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -27..-1 <400> 948 Met Leu Phe Trp Leu Pro Ser Pro Ser Glu Thr Thr Ser Ala Trp Thr -25 -20 -15 Leu Leu Ser Ile Ser Leu Ser Val Phe Trp Ser Glu Pro Phe Asn Lys -5 1 Ser Leu Gly Ser Ser Lys Leu Pro Cys His Phe Phe Ser Ile Lys Arg 10

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15

Ile Ser Lys Ile His Pro Ser His Pro Pro 25

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 <211> 74
 <212> PRT
 <213> Homo sapiens
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Met Phe Phe Leu Asn Ile Ala Met Phe Ile Val Val Met Val Gln Ile
                       -45
                                           -40
Cys Gly Arg Asn Gly Lys Arg Ser Asn Arg Thr Leu Arg Glu Glu Val
-35
                   -30
                                      -25
Leu Arg Asn Leu Arg Ser Val Val Ser Leu Thr Phe Leu Leu Gly Met
               -15
                                   -10
                                                    - 5
Thr Trp Gly Phe Ala Phe Phe Ala Trp Gly Pro Leu Asn Ile Pro Phe
           1
                        5
                                              10.
Met Tyr Leu Phe Ser Ile Phe Asn Ser Leu
                       20
<210> 954
<211> 58
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 954
Met Asn Lys His Phe Leu Phe Leu Phe Leu Leu Xaa Xaa Leu Ile Val
    -15
             -10
Ala Val Thr Ser Leu Gln Cys Ile Thr Cys His Leu Arg Thr Arg Thr
  1
                5
                                       10
Asp Arg Cys Arg Arg Gly Phe Gly Xaa Cys Thr Ala Gln Lys Gly Glu
               20
Ala Cys Met Leu Leu Arg Ile His Gln Arg
           35
<210> 955
<211> 47
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -35..-1
<400> 955
Met Tyr Ile Lys Met Glu Ser Val Thr Leu Ser Pro Ala Pro Val Phe
-35
                  -30
                                      .-25
Pro Val Pro Ala Gln Leu Leu Leu Thr Ser His Phe Leu Gly Glu
              -15
                                 -10
Ser Leu Gly Gly Gly Thr Leu Leu Val Pro Leu Leu Pro Pro Gly
                                              10
<210> 956
<211> 40
<212> PRT
<213> Homo sapiens
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<220>
 <221> SIGNAL
 <222> -27..-1
 <400> 956
 Met Xaa Xaa Ala Leu Leu Arg Ser Arg Met Ile Gln Gly Arg Ile Leu
                             -20
                                                -15
 Leu Leu Thr Ile Cys Ala Ala Gly Ile Xaa Gly Thr Arg Gln Phe Gly
                         -5
                                             .1
 Tyr Asn Leu Ser Ile Ile Asn Asp
                 10
<210> 957
 <211> 54
<212> PRT
 <213> Homo sapiens
<220>
<221> SIGNAL
<222> -47..-1
<400> 957
Met Met Gly Xaa Leu Cys Pro Arg Ser Leu Pro Ile Pro Pro Met Ile
        -45
                            -40
Leu Ser Trp Trp Lys Met Gln Trp Lys Pro Leu Ala Leu Glu Asn Phe
  -30
                        -25
                                            -20
Ser Gly Ser Cys Leu Phe Ser Xaa Ala Trp Leu Xaa Cys Xaa Cys His
-15
                    -10
Gly Asp Asp Leu Ser
<210> 958
<211> 48
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 958
Met Gly Leu Leu Gln Leu Leu Ala Phe Ser Phe Leu Gly Asn Ser Val
                   -10
                                        -5
Glu Thr Val Arg Gly Gly Gly Arg Thr Trp Ala Trp Gly Arg Lys Thr
                               10
Gln Lys Leu Leu Ala His Leu Arg Gly Ile Leu Gly Ala Trp Xaa Arg
                                                30
<210> 959
<211> 25
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
<400> 959
Met Leu Val Leu Val His Ser Ser Leu Ser Lys Thr Leu Ser Gln Lys
               -10
Lys Lys Phe Thr Xaa Pro Thr Arg
```

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<210> 960
  <211> 48
  <212> PRT
  <213> Homo sapiens
  <220>
 <221> SIGNAL
  <222> -19..-1
  <400> 960
  Met Ser Phe Ser Ser Ala Leu Ile Leu Val Ile Ser Cys Leu Leu Leu
                                      -10
  Ala Phe Glu Cys Val Cys Ser Cys Phe Ser Gly Ser Phe Asn Cys Asp
                             5
  Val Arg Val Ser Ile Ser Asp Leu Ser Cys Phe Leu Leu Trp Gly Lys
                          20
  <210> 961
  <211> 28
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -22..-1
  <400> 961
  Met Gly Phe Trp Cys Gly Cys Pro Phe Cys Leu Xaa Val Phe Leu Leu
                            -15
  Thr Asp Arg Thr Leu Ser Cys Arg Ser Val Gly Val
  <210> 962
  <211> 27
 <212> PRT
  <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -15..-1
 <400> 962 -
 Met Val Leu Leu Ser Leu Ser Leu Trp Gly Ile Ser Thr Leu Ser Ser
 -15
                     -10
                                         - 5
 Thr Thr Ile Glu Leu Ile Tyr Thr Pro Ile Gly
             5
 <210> 963
 <211> 28
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -25..-1
<400> 963
 Met Ala Ser Leu Leu Ser Gly Phe Thr Ser Phe Cys Leu Leu His Val
                    -20
                                     -15
 His Ser Phe Leu Pro Pro Val Phe Ser Thr Gln Asn
                - 5
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<221> SIGNAL

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<211> 42
 <212> PRT
 <213> Homo sapiens
 <220>
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 <222> -30..-1
 <400> 964
 Met Glu Thr Ala Leu Xaa Xaa Thr Pro Gln Lys Arg Gln Val Met Phe
                     -25
                                        -20
 Leu Ala Ile Leu Leu Xaa Xaa Trp Glu Ala Gly Ser Glu Ala Val Arg
             -10
                                     - 5
 Tyr Ser Ile Pro Glu Glu Thr Glu Ser Gly
       5
                             10
 <210> 965
 <211> 66
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -35..-1
 <400> 965
 Met Met Leu Asp Phe Ala Leu Ser Pro Arg Leu Glu Arg Ser Gly Leu
                -30
                                        -25
 Ile Met Ala Cys Cys Thr Leu Asp Leu Leu Gly Ser Ser Ser Pro Pro
                -15
                                    -10
 Thr Ser Ala Ser Gln Val Ala Gly Thr Gly His Val Pro Pro His Pro
 Ala Ser Phe Phe Tyr Phe Xaa Val Xaa Gln Val Tyr Tyr Val Ser Gln
                       20
 Leu Ile
 30
 <210> 966
<211> 64
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1
<400> .966
Met Arg Thr Pro Gln Leu Ala Leu Leu Gln Val Phe Phe Leu Val Phe
        -20
                           ~15
                                                -10
Pro Asp Gly Val Arg Pro Gln Pro Ser Ser Ser Pro Ser Gly Ala Val
                       1
Pro Thr Ser Leu Glu Leu Gln Arg Gly Thr Asp Gly Gly Thr Leu Gln
             15
                                   20
Ser Pro Ser Glu Ala Thr Ala Thr Arg Pro Ala Val Pro Gly Leu Arg
            30
                                35
<210> 967
<211> 46
<212> PRT
<213> Homo sapiens
<220>
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<222> -21..-1
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<400> 967

Met Pro Arg Pro Arg Ala Cys Ala Ser Trp Pro Leu Leu Ala Ala Val

Ser Gly Leu Arg Gly Leu Glu Trp Pro Pro Ser Trp Arg Arg Val Val

Ala Ala Val Gly Val Cys Arg Val Arg Asp Trp Gly Pro Arg

<210> 968.

<211> 23

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -17..-1

<400> 968

Met Asn Gly Ile Phe Leu Leu Leu Ile Ser Val Leu Thr Val Ile Trp
-15 -10 -5

Phe Trp Lys Thr His Pro Gly
1 5

<210> 969

<211> 27

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -18..-1

<400> 969

Met Val Phe Leu Val Xaa Leu Leu Cys Ile Ile Xaa Leu Tyr Leu Ile

Arg Gly Ser Glu Trp Xaa Leu Pro Pro Asn Trp

<210> 970

<211> 53

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -18..-1

<400> 970

Met Met Thr Leu Ala Leu Phe Phe Leu Leu Arg Ile Ala Leu Ala Ser -15 -10 -5

Trp Ala Leu Phe Trp Ile His Met Asn Phe Arg Arg Ala Phe Phe His  $1 \hspace{1.5cm} 5 \hspace{1.5cm} 10$ 

Leu Arg Trp Phe Asp Ile Asn Ser Thr Glu Ser Val Asn Cys Phe Gly 25 30

Gln Tyr Gly Leu Ala

<210> 971

<211> 37

<212> PRT

<213> Homo sapiens

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<220>
 <221> SIGNAL
 <222> -29..-1
 <400> 971
 Met Ser Ile Arg Ser Asn Trp Ser Ser Val Glu Ser Lys Ser Arg Ile
             -25
                    -20
                                         -15...
 Ser Leu Leu Val Phe Cys Leu Asn Asp Leu Ser Asn Ala Val Xaa Xaa
    -10
 Gly Ile Glu Xaa Pro
    5
 <210> 972
 <211> 120
 <212> PRT
<213> Homo sapiens
 <220>
 <221> SIGNAL
<222> -16..-1
<400> 972
Met Ala Trp Ile Pro Leu Phe Leu Gly Val Leu Ala Tyr Cys Thr Gly
                       -10
Ser Val Ala Ser Tyr Glu Leu Thr His Pro Pro Ser Val Ser Val Ser
                                   10
Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp
           20
Lys Tyr Ala Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu
                           40
Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
                       55
                                          60
Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr
                   70
                                      75
Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser
               85
                                   90
Thr Val Val Phe Gly Gly Gly Thr
           100
<210> 973
<211> 32
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -29..-1
<400> 973
Met Val Cys Val Ile Phe Lys Glu Leu Met Glu Phe Glu Phe Pro Gly
              -25 -20
Phe Cys Phe Xaa Leu Cys Phe Gly Arg Ser Ser Leu Cys Cys Arg Xaa
<210> 974
<211> 78
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
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<400> 974
 Met Glu Ser Ser Gly Thr Pro Ser Val Thr Leu Ile Val Gly Ser Gly
                    -25
                                   -20
 Leu Ser Cys Leu Ala Leu Xaa Thr Leu Ala Val Val Tyr Ala Ala Leu
                 -10
                                     -5
 Trp Arg Tyr Ile Arg Ser Glu Arg Ser Ile Ile Leu Ile Asn Phe Cys
                             10
                                           . 15
 Leu Ser Ile Ile Ser Ser Asn Ile Leu Ile Leu Val Gly Gln Thr Gln
                        25
 Thr His Asn Lys Glu Tyr Leu His Asn His His Cys Ile Phe
                    40
 <210> 975
 <211> 58
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -31.:-1
 <400> 975
 Met Gly Val Cys Cys Ala Gln Asn Cys Ser Val Ser Gly Xaa Xaa Arg
                        -25
                                            -20
 Asn Ala Leu Xaa Phe Leu Ala Ser Ser Phe Cys Phe Gly Glu Ala Asp
 -15
                    -10
                                        - 5
 Ser Gly Ser Arg Cys Cys Leu Lys Ile Ile Leu Gly Phe Tyr Leu Ile
                               10
Arg Tyr Ser Leu Ile Thr Tyr Gln Val Arg
        20
<210> 976
<211> 40
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 976
Met Lys Ile Leu Tyr Leu Phe Phe Phe Leu Lys Trp Ser His Pro Gly
           -15
                         -10
Trp Ser Ala Thr Xaa Trp Ser Trp His Thr Ala Thr Ser Ala Ser Leu
Ile Gln Val Ile Leu Pro Pro Trp
<210> 977
<211> 34
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 977
Met Thr Pro Cys Phe Leu Gln Met Asp Asn Leu Thr Pro Leu Phe Leu
                       -20
                                            -15
Ser Gly Cys Phe Leu Phe Leu Ser Xaa Cys Xaa Ile Tyr Leu Ala Arg
-10
                   - 5
```

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487
Ile Leu
<210> 978
 <211> 48
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
<222> -40..-1
<400> 978
Met Gly Ser Ala Gly Arg Leu His Tyr Leu Xaa Met Thr Ala Glu Asn
                   -35
                                       -30
Pro Thr Pro Gly Asp Leu Ala Pro Xaa Pro Leu Ile Thr Cys Lys Leu
                -20
                     -15
Cys Leu Cys Glu Gln Ser Xaa Gly Gln Asp Asp His Thr Pro Gly Met
                               1
<210> 979
<211> 88
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -49..-1
<400> 979
Met Asn His Leu Pro Pro Asn His Tyr Arg Xaa His Val Phe Thr Cys
                -45
                                   -40
His Val Asp Gln Tyr Leu Thr Val Glu Thr Ala Gly Gly Met Glu Lys
           -30
                               -25
Glu Ala Val Ser Val Thr Val Leu Leu Ser Ala Ala Pro Cys Leu Leu
       -15
                          -10
                                              -5.
Ser Cys Phe Leu Gly Ser Ser Val Ser Gly Leu Ala Phe Trp Val Ser
                                      10
Gln Gln Lys Thr Lys Gly Pro Glu Arg Cys Lys Asn Thr His His Xaa
              20
                                   25
Ala Xaa Asn Asn Phe Pro Ala Arg
<210> 980
<211>, 42
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -40..-1
<400> 980
Met Asn Lys Ile Lys Glu Asn Thr His Thr His Thr His Thr
                  -35
                                   -30
His Lys Asn Asn Thr Lys Leu Val Ser Asn Leu Phe Leu Phe Met Leu
              -20
                                  ~15
Pro Leu Trp Cys Ser Ile Gly Thr Cys Thr
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<210> 981 <211> 51 <212> PRT <213> Homo sapiens

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<220>
 <221> SIGNAL
 <222> -42..-1
 <400> 981
 Met His Asp Ser Ser Gly Lys Asn Asn Phe Arg Lys Ile Pro Val Val
        -40
                           -35
                                        -30 ·
 Asn Leu Ile Tyr Leu Tyr Val Asp Ile His Ile His Lys Leu Phe Leu
                      -20
                                            -15
 Tyr Ser Leu Phe Thr Glu Asn Val Leu Ala His Pro Cys Ile Val Leu
 -10
 Arg Arg Leu
 <210> 982
 <211> 37
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -33..-1
 <400> 982
 Met Gly Arg Leu His Arg Pro Arg Ser Ser Thr Ser Tyr Arg Asn Leu
           -30 -25
                                                -20
 Pro His Leu Phe Leu Phe Leu Phe Val Gly Pro Phe Ser Cys Leu
       -15
                            -10
 Gly Ser Tyr Ser Arg
    1
 <210> 983
 <211> 44
 <212> PRT
 <213> Homo sapiens
<220>
 <221> SIGNAL
 <222> -27..-1
 <400> 983
 Met Gln Ser Gln Ala Ala Arg Glu His Lys Pro Gly Xaa Ser Arg Leu
                            - 2.0
                                               -15
 Leu Leu Leu Leu Leu Xaa Leu Pro Leu Pro Pro Pro Xaa Leu Arg
                       - 5
                                           1
 Thr Arg Xaa Phe Ser Xaa Thr Thr Leu Thr Ala Gly
                10
<210> 984
<211> 25
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 984
Met Arg Leu Trp Ser Leu Ala Cys Leu Ser Pro Pro Ala Val Gln Leu
                   -10
                                       - 5
Gly Ser Gln Gln Ala Thr Asp Trp Trp
```

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<210> 985
 <211> 32
  <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -25..-1
 <400> 985
 Met Ser Pro Leu Phe Ile Leu Ile Val Leu Ile Trp Ile Phe Ser Phe
 -25 -20
                              -15
 Phe Phe Phe Ile Thr Leu Val Arg Gly Ser Ile Asn Leu Phe Phe
                -5
 <210> 986
 <211> 25
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -22..-1
 <400> 986 -
 Met Asn Leu Gly Gly His Ser Asp His Ser Thr Phe Leu Phe Phe Leu
     -20
                            -15
 Phe Phe Ser Val Phe Cys Phe Phe
 <210> 987
 <211> 91
 <212> PRT
 <213> Homo sapiens
 <220>
<221> SIGNAL
 <222> -21..-1
 <400> 987
 Met Leu Asp Phe Ala Ile Phe Ala Val Thr Phe Leu Leu Ala Leu Val
                       -15
                                          -10
 Gly Ala Val Leu Tyr Leu Tyr Pro Ala Ser Arg Gln Ala Ala Gly Ile
                   1
 Pro Gly Ile Thr Pro Thr Glu Glu Lys Asp Gly Asn Leu Pro Asp Ile
            15
                               20
 Val Asn Ser Gly Ser Leu His Glu Xaa Leu Val Asn Leu His Glu Arg
       30
                           35
 Tyr Gly Pro Val Val Ser Phe Trp Phe Gly Arg Arg Leu Val Val Ser
                       50
Leu Gly Thr Val Asp Val Leu Lys Gln His Arg
                   65
 <210> 988
 <211> 28
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 988
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Met Ala His Cys Ser Leu Glu Leu Leu Gly Ser Ser Pro Pro Ile
                      -10
             -15
  Ser Ala Ser Gln Ser Thr Gly Ile Thr Ser Val Ser
                        5
  <210> 989
  <211> 44.
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -17..-1
 <400> 989
 Met Pro Ser Gln Leu Leu Leu Ser Leu Ser Leu Phe Leu Phe Phe
      -15
                     -10
                                               -5
  Trp Arg Gln Ser Leu Val Leu Trp Pro Arg Leu Glu Cys Ser Cys Val
   1
                  5
                                        10
 Ile Ala Ala His Cys Ser Leu Thr Ser Gln Ala Arg
                 20
 <210> 990
 <211> 83
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
 <222> -46..-1
 <400> 990
 Met Tyr Thr Asn Lys Tyr Thr Leu Ile Tyr Asn Ile Leu Ile Tyr Asn
   -45
                        -40
                                           -35
 Ile Cys Xaa Xaa Tyr Met Trp Leu Ile Leu Ile Tyr Met Tyr Leu His
 -30
                    -25
                                       -20
                                                          -15
Ile Cys Leu Phe Cys Cys Xaa Phe Ile Ser Ser Cys Asn Ser Val Phe
                -10
 Pro Cys Val Ile Xaa Phe Leu Leu Pro Glu Glu Leu Leu Xaa Val Xaa
                         10
                                               15
 Leu Xaa Xaa Xaa Phe Xaa Val Arg Trp Ser Leu Xaa Xaa Ser Ser Arg
   20
                        25
 Leu Glu Cys
 35
 <210> 991
 <211> · 35
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -31..-1
 <400> 991
 Met Leu Leu Thr His Asn Glu Asp Tyr Met Pro Gly Asn Xaa Xaa
                       -25
                                          -20
 Xaa Xaa Leu Trp Ser Leu Ile Gln Ala Val His Ile Cys Leu Gly Arg
 -15
             -10
                                       - 5
 Lys Lys Lys
 <210> 992
 <211> 89
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491
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -19..-1
 <400> 992
 Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
                -15
                                     -10
 Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Leu Val Lys
 Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
                        20
Ser Asp Tyr Xaa Xaa Thr Xaa Ile Arg Xaa Ala Xaa Gly Lys Gly Leu
                                         40
Xaa Trp Ile Xaa Xaa Ile Thr Thr Ser Gly Asn Thr Ala Xaa Tyr Ala
                50
                                     55
                                                         60
Xaa Ser Val Lys Xaa Arg Phe Thr Ile
            65
<210> 993
<211> 55
<212> PRT
<213> Homo sapiens
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<222> -17..-1
<400> 993
Met Lys Arg Phe Phe Leu Phe Val Cys Leu Xaa Phe Asp Glu Ser Cys
        -15
                           -10
Ser Val Thr Arg Leu Gly Cys Cys Gly Ala Ile Ser Ala His Cys Xaa
                                       10
Leu Arg Leu Pro Gly Ser Ser Xaa Xaa Pro Ala Ser Thr Ser Arg Val
               20
                                    25
Xaa Gly Ile Thr Gly Met Arg
            35
<210> 994
<211> 40
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -38..-1
<400> 994
Met Ser Cys His Ser Leu Leu Ala Cys Lys Val Phe Thr Glu Lys Ser
          -35
                               -30
                                                   -25
Pro Thr Lys His Ile Arg Glu His His Cys Met Leu Phe Val Ser Phe
  -20
                           -15
Leu Leu Leu Leu Gly Ser Arg
   -5
<210> 995
<211> 50
<212> PRT
<213> Homo sapiens
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<220>

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Glu Ser

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492
  <221> SIGNAL
  <222> -26..-1
 <400> 995
 Met Thr Ser Ser Val His Leu Leu Val Phe Lys Asp His Leu Leu Ser
   -25
                         -20
                                             -15
 Met Leu Ser Cys Cys Gln Gly Ala Cys Cys Pro Ser Thr Pro His Glu
                     - 5
                                         1
 Gly Thr Arg Ser Thr Val Ser Trp Ile Pro Pro Thr Tyr Lys Ala Ala
             10
                                 15
 Thr Gln
<210> 996
 <211> 23
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -19..-1
 <400> 996
 Met Val Arg Ala Ser Ile Leu Leu Ser Met Phe Cys Val Ser His Thr
                -15
                                    -10
 Val Gln Thr Ala Thr Tyr Thr
<210> 997
 <211> 52
 <212> PRT
 <213> Homo sapiens
<220>
 <221> SIGNAL
<222> -17..-1
<400> 997
Met Glu Lys Thr Ala Leu Ser Ser Phe Thr Trp Trp Ala Pro Ala Cys
        -15
                           -10
                                              - 5
Cys Ala Pro Arg Thr Tyr Val Val Ser Ala Thr Thr Leu Ser Ala Val
                                       10
Gln Gly His Cys Pro Leu Gln Ser Arg Thr Ser Thr Lys Gly Lys Leu
                           25
Trp Pro Phe Gly
            35
<210> 998
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 998
Met Ile Phe Thr Phe Gln Gln Ile Gly Gly Lys Leu Leu Ser Gly
           -20
                               -15
Leu Thr Gln Glu Cys Leu Gly Ala Leu Pro Glu Ala Asn Val Phe Cys
    - 5
Arg Gly Gly Cys Thr Ala Thr Val Leu Lys His Gly Lys Ala Ser Pro
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20

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<210> 999
 <211> 46
 <212> PRT.
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -31..-1
 <400> 999
 Met Asn Cys Val Arg Gln Ala Asn Ile Arg Met Gln Cys Lys Ile Tyr
    -30
                         -25
                                            -20
Asp Ser Leu Leu Ala Leu Ser Pro Asp Leu Gln Ala Ala Arg Gly Leu
                    ~10
                                        - 5
 Met Cys Ala Ala Ser Val Met Ser Phe Leu Ala Phe Met Met
     . 5
                                10
<210> 1000
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -40..-1
<400> 1000
Met Ile Trp Leu Ser Phe Cys Leu Leu Leu Val Tyr Arg Asn Ala Cys
                   -35
                                        -30
Asp Phe Cys Thr Leu Thr Leu Tyr Pro Gly Thr Leu Leu Lys Leu Leu
                -20
                                    -15
Ile Ser Leu Arg Ser Phe Trp Ala Glu Thr Thr Gly
<210> 1001
<211> 43
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 1001
Met Phe Ser Ser Pro Gly Leu Arg Thr Leu Phe Val Leu Val Gly Ser
                   -20
                                       -15
Leu His Leu Phe Leu Ser Val Leu Ala Ser Lys Ser Arg Asn Ser Lys
               - 5
                                   1
Lys Gln Arg Leu Phe Leu Leu Val Pro Leu Tyr
      10
<210> 1002
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 1002
Met Leu Thr Asp Gly Ile Leu Met Arg Val Asn Val Cys Ser Leu Pro
```

```
-20
                                   -15
   Ala Pro Gly Leu Cys Ser Gly Gln Pro Gly Val Arg Ala Trp Pro Gly
          - 5
   Val Thr Gln Leu Thr Gln Xaa Glu Glu Cys Pro Trp Phe Ser Ala Leu
                       15
                                          20
   Glu Gly Leu
  <210> 1003
   <211> 49
   <212> PRT
   <213> Homo sapiens
  <220>
   <221> SIGNAL
   <222> -33..-1
  <400> 1003
  Met Phe Asn Trp Asn Pro Trp Leu Thr Thr Leu Ile Thr Gly Xaa Ala
              -30
                                  -25 .
  Gly Pro Leu Leu Ile Leu Leu Ser Leu Ile Phe Gly Pro Cys Ile '
       -15
                              -10
  Leu Asn Ser Phe Leu Asn Xaa Ile Lys Gln Arg Ile Ala Ser Gly Lys
                      5
                                          10
  Arg
  <210> 1004
  <211> 102
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -29..-1
  <400> 1004
  Met Ala Gly Ser Arg Gln Arg Gly Leu Arg Ala Arg Val Arg Pro Leu
                  -25
                                      -20
  Phe Cys Ala Leu Leu Ser Leu Xaa Xaa Xaa Pro Xaa Xaa Arg
              -10
                                  -5
  Arg Xaa Arg Arg Pro Arg Gly Arg Val Ala Thr Ser Pro Phe Arg Val
                         10
                                              15
  Xaa Ile Gln Leu Gln Gly Ala Ala Pro Gly Ala Glu Arg Arg Asp Arg
                                         30
  Ala Leu Leu Gly Pro Arg Gly Glu Cys Tyr Ser Lys Phe Arg Ser Asn
                                     45
  Ser Ser Ser Thr Ile Phe Lys Lys Xaa Lys Arg Leu Ser Val Xaa Xaa
             55
                                  60
  Asp Xaa Ser Gly Pro Gly
        70
  <210> 1005
  <211> 96
  <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -19..-1
 <400> 1005
 Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Leu Lys Gly
                 -15
                                     -10
. Val His Cys Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
```

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Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Leu Thr Leu
                         20
Ser Asn Asp Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
30
Val Trp Val Ser His Ile Asp Ser Ser Xaa Thr Ile Thr Asn Tyr Ala
                 50
                                     55
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Trp
<210> 1006
<211> 38
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -15..-1
<400> 1006
Met Gly Leu Phe Leu Gly Phe Leu Ala Cys Ser Val Ala Tyr Gln Cys
                    -10
His Ser Ala Phe Val Thr Val Ala Ser Gln Tyr Thr Leu Lys Ser Glu
                                 10
Thr Leu Met Pro Ala Ala
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<210> 1007
<211> 104
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -49...-1
<400> 1007
Met Trp Glu Asp Ser Arg Asn Lys Arg Gly Gly Arg Trp Leu Val Ser
                -45
                                     -40
Leu Ala Lys Gln Gln Arg His Ile Glu Leu Asp Arg Leu Trp Leu Glu
            -30
                                -25
Thr Phe Ser Val Phe Leu Gly Leu Ile Phe Phe Leu Glu Leu Ala Thr
        -15
                            -10
Gly Ile Leu Ala Phe Val Phe Lys Asp Trp Ile Arg Asp Gln Leu Asn
                    5
Leu Phe Ile Asn Asn Asn Val Lys Ala Tyr Arg Asp Asp Ile Asp Leu
                                    25
Gln Xaa Leu Ile Asp Phe Ala Gln Glu Tyr Trp Ser Cys Cys Gly Xaa
           35
Glu Ala Pro Ile Xaa Gly Thr Gly
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<210> 1008
<211> 34
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -14..-1
<400> 1008
Met Phe Leu Ser Leu Ser Thr Ala Phe Trp Val Val Tyr Ala Met Ile
```

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-10
                                   - 5
 Ile Tyr Ser Ala Leu Ser Ala Gly Phe Ile Ile Phe Phe Leu Val Val
                             10
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 Phe Asn
   20
 <210> 1009
 <211> 38
 <212> PRT
 <213> Homo sapiens
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<221> SIGNAL
 <222> -34..-1
<400> 1009
Met Tyr Ile Val Met Asp Leu Pro Leu Trp Leu Ser His Glu Val Gln
                -30
                                    -25
Ser Tyr Ile Pro Ser Phe Phe Leu Phe Phe Cys Phe Glu Thr Gly Ser
            -15
                                 -10
His Ser Val Thr His Gly
       . 1
<210> 1010
<211> 54
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -27..-1
<400> 1010
Met Val Ala His Asp Tyr Gln Asn Ile Ile Ser Leu Phe Phe Leu Ala
                            -20
Phe Ser Phe Ser Phe Pro Ser Ser Phe Ser Ser Phe Phe Leu Xaa
                        -5
                                            1
Phe Leu Ser Phe Phe Ser Ser Phe Phe Leu Ser Leu Leu Ser Phe Pro
               10
                                    15
Ser Phe Leu Pro Pro Gly
            25
<210> 1011
<211> 136
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -15..-1
<400> 1011
Met Ala Ala Leu Arg Ala Leu Cys Gly Phe Arg Gly Val Ala Ala Gln
                   -10
Val Leu Arg Xaa Gly Ala Gly Val Arg Leu Pro Ile Gln Pro Ser Arg
                                10
Gly Val Arg Gln Trp Gln Pro Asp Val Glu Trp Ala Gln Gln Phe Gly
                           25
Gly Ala Val Met Tyr Pro Ser Lys Glu Thr Ala His Trp Lys Pro Pro
                       40
                                            45
Pro Trp Asn Asp Val Asp Pro Pro Lys Asp Thr Ile Val Lys Asn Ile
                                        60
Thr Leu Asn Phe Gly Pro Gln His Pro Ala Ala His Gly Val Leu Arg
```

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·75
                                                     80
 Leu Val Met Glu Leu Ser Gly Glu Met Val Arg Lys Cys Asp Pro His
                              90
                                             95
 Ile Gly Leu Leu His Arg Gly Thr Glu Lys Leu Ile Glu Tyr Lys Xaa
                           105
 Tyr Leu Gln Ala Leu Pro Tyr Phe
    115
                       120
 <210> 1012
 <211> 50
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
 <222> -28..~1
 <400> 1012
Met Leu Ile Trp Ser Ser Ser Phe Pro Ala Pro Pro Leu Phe Leu
           -25
                                   -15
                              -20
 Val Phe Leu His Leu Phe Leu Xaa Val Tyr Leu Gly Leu Val Met Pro
     -10
                          -5
                                            1
Thr Gln Gln Tyr Leu Leu Cln Ser Pro Leu Met Phe Thr Asp Lys
                  10
                                     15
Ala Gln
<210> 1013
<211> 57
<212> PRT
<213> Homo sapiens
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<222> -46..-1
<400> 1013
Met Cys Arg Met Cys Arg Phe Val Thr Trp Ile Asn Val Cys His Gly
 -45
               -40
                                        -35
Asp Leu Leu His Arg Ser Ser Arg Arg Leu Gly Val Lys Pro Ser Thr
               -25 -20
His Trp Leu Phe Phe Leu Met Leu Ser Leu Cys Thr Pro Pro Asp Arg
              -10
Pro Trp Cys Val Leu Phe Pro Pro Leu
                         10
<210> 1014
<211> 40
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -31..-1
<400> 1014
Met Xaa Thr Gln Glu Ala Gly Leu Ile Phe Phe Ser Pro Pro Phe Ser
                     -25 -20
Leu Ser Leu Ser Leu Pro Leu Ser Leu Xaa Leu Leu Xaa Xaa
-15 -10
                                · -5
Pro His Ser Arg Thr Pro Gln Arg
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<221> SIGNAL

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<211> 43
 <212> PRT
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 <220>
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 <222> -13..-1
 <400> 1015
 Met Glu Phe Leu Leu Trp Ser Leu Xaa Ser Asn Gly Lys Arg Gly
            -10
                                - 5
 Gln Ala Trp Arg Leu Met Pro Val Val Pro Ala Val Trp Glu Pro Glu
                        10 .
Ala Gly Gly Leu Leu Gln Leu Gly Gly Ser Arg
                    25
<210> 1016
<211> 88
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 1016
Met Met Val Thr Tyr Arg Trp Gly Phe Gly Val Asp Val Xaa Phe Val
        -35
                            -30
                                                -25
Ala Val Asp Ala Ile Pro Phe Cys Leu Leu Val Phe Phe Leu Ile Val
                        -15
                                            -10
Arg Thr Leu Ser Cys Arg Ser Val Gly Val Cys Trp Arg Ser Thr Pro
Asp Pro Val Cys Leu Gly Ile Thr Ser Arg Gly Cys Arg Thr Glu Ile
                                20
Leu Gln Asn Ser Lys Cys Cys Ser Leu Ile Leu Pro Leu Glu Ala Ser
       30
Ser Gln Arg Gly Thr Glu Cys Met
  45
<210> 1017
<211> 34
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 1017
Met Leu Tyr Pro Leu Pro Glu Ile Phe Leu Pro Phe Ser Leu Ser Pro
               -15
                                   -10
Ala Asn Ala Gln Ser Lys Phe Ser Leu Tyr Phe Phe Pro Leu Val Lys
Pro Gly
   15
<210> 1018
<211> 48
<212> PRT
<213> Homo sapiens
<220>
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<222> -27..-1
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<400> 1018

Met Ser Leu Glu Pro Ala Ser Xaa Leu Leu Gly Val Arg Arg Arg Leu
-25 -20 -15

Leu Cys Leu Xaa Phe Xaa Arg Leu Leu Cly Thr Ser Leu Leu Lys

Phe Val Xaa Ser Xaa Ser Pro Pro Xaa Pro Xaa Thr Leu Thr Ser Ser 10 15 20

<210> 1019

<211> 33

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -24..-1

<400> 1019

Met Leu Ile Leu Tyr Leu Ala Thr Leu Leu Asn Leu Ser Val Leu Ile'
-20 -15 -10

Leu Cys Val Cys Val Cys Val Tyr Asp Leu Tyr Ile Xaa Arg

Gly

<210> 1020

<211> 117

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -16..-1

<400> 1020

Met Ala Pro Leu Gly Thr Thr Val Leu Leu Trp Ser Leu Leu Arg Ser
-15 -10 -5

Ser Pro Gly Val Glu Arg Val Cys Phe Arg Ala Arg Ile Gln Pro Trp
1 5 10 15

His Gly Gly Leu Leu Gln Pro Leu Pro Cys Ser Phe Glu Met Gly Leu 20 25 30

Pro Arg Arg Phe Ser Ser Glu Ala Ala Glu Ser Gly Ser Pro Glu
35

Thr Lys Lys Pro Thr Phe Met Asp Glu Glu Val Gln Ser Ile Leu Thr 50 55 60

Lys Met Thr Gly Leu Asn Leu Gln Lys Thr Phe Lys Pro Ala Ile Gln 65 70 75 80

Glu Leu Lys Pro Pro Thr Tyr Lys Leu Met Xaa Gln Ala Gln Leu Glu
85 90 95

Glu Ala Thr Arg Gln 100

<210> 1021

<211> 99

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -34..-1

<400> 1021

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Met Leu Leu Thr Phe Ser Ser Ser Arg His Arg Arg Leu Tyr Arg
                                -25
Arg Arg His His Leu Leu Phe Val Val Leu Leu Pro Pro Pro
                               -10
Gly Ser Val Xaa Leu Cys Ser Xaa Xaa Xaa Xaa Val Leu Xaa Xaa
                       5 '
Xaa Lys Phe Arg Xaa Gly Leu His Gly Ala Met Leu Pro Gly Leu Phe
                   20
                                       25
Arg Gly Arg Pro Arg Ala Ala Leu Arg Leu Arg Val Ser Pro Xaa Cys
               35
                                   40
Pro Gly Trp Lys Val Ala Arg Ser Arg Leu Thr Ala Thr Ser Ala Ser
Arg Xaa Arg
     65
<210> 1022
<211> 32
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 1022
Met Leu Leu Leu Gln Leu Asn Leu Lys Thr Leu Ser Ser Ser Thr
           -10
                             - 5
Ile Ala Leu Lys Lys Ile Ser Gly Glu Leu Leu Arg Lys Arg Lys Arg
                       10
<210> 1023
<211> 18
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 1023
Met Ser Leu Phe Val Leu Leu Ile Ile Thr Gln Leu Leu Tyr Gly Gly
-15
                   -10
Ile Leu
<210> 1024
<211> 34
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -28..-1
<400> 1024
Met Asn Cys Phe Cys Asn Phe Val Lys Thr Ser Glu Ala Tyr Met Ile
          -25
                              -20
                                                  -15
Leu Phe Leu Gly Val Leu Leu Ser Ala Ser Asp Leu Cys Val Tyr Pro
Ile Gly
<210> 1025
<211> 33
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<212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -14..-1
 <400> 1025
 Met Ser Val Ile Leu Ala Leu Trp Glu Ala Glu Ala Gly Gly Ser Pro
                 -10
                                     - 5
 Glu Ile Gly Ser Ser Gly Pro Ala Ala Pro Thr Trp Arg Ser Pro Val
         5
                          . 10
 Gln
 <210> 1026
 <211> 61
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -29..-1
<400> 1026
Met Tyr Gly Glu Ser Thr Leu Phe Ile His Ser Ser Val His Gly His
                -25
                                     -20
                                                         -15
Leu Gly Cys Leu Leu Leu Ala Val Arg Ser Ser Ala Thr Val Asn Ile
            -10
                                 -5
                                                    1
Thr Tyr Xaa Xaa Val Cys Val Asp Ile Xaa Xaa His Phe His Met Leu
                         10
                                             15
Met Ser Gly Ile Thr Gly Ser Tyr Gly Asn Ser Leu Ser
                     25
<210> 1027
<211> 74
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -51..-1
<400> 1027
Met Ala Ala Ser Val Leu Asn Thr Val Leu Arg Arg Leu Pro Met Leu
                        -45
                                             -40
Ser Leu Phe Arg Gly Ser His Arg Val Gln Val Thr Leu Arg Lys Thr
-35
                    -30
                                        -25
Phe Cys Thr Thr Ser Ser Trp Leu Tyr Leu Leu Glu Val Val Ala Pro
                -15
                                    -10
Leu Ser Gly Ile His Glu Trp Arg Pro Ser His Val Cys Leu Ser Cys
           . 1
                            5
                                                10
Leu Gly Ser Thr Ser Cys Asn Pro Pro Glu
    15
<210> 1028
<211> 84
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -65..-1
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<400> 1028
  Met Leu Arg Ser Ala Cys Val Ser Gln His Ala Gly Gly Ile Trp Val
                     -60
                                         -55
  Asp Arg Gly Gly Pro Gln Cys Gln Arg Val Phe Thr Phe Cys Arg Gly
                  -45
                                     -40
                                                    -35 (
  Leu Ser Pro Asn Phe Gly Arg Ser Glu Thr Gln Arg Glu Arg Trp Ile
             -30
                                 -25
                                                     -20
  Arg Pro Gly Gln Leu Met Val Val Ala Glu Thr Ser Gln Gly Ser Trp
   -15
                             -10
  Ser Ala Pro Thr Ser Pro Xaa Thr Ser Cys Pro Pro Pro Asn Thr Xaa
    1
                   5
                                         1.0
 Thr Thr Pro Xaa
 <210> 1029
 <211> 94
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -45..-1
 <400> 1029
 Met Val Ser Arg Ser Leu Arg Gly Arg Arg Thr Trp Val Arg Cys Met
                    -40
                                        -35
 Arg Arg Leu Pro Pro Ile Pro Ala Trp Ser Gln Gly Lys Gly Met Pro
                -25
                                    -20
 Gly Phe Val Ser Leu Leu Val Val His Ala Ala Asp Ala Trp Val Ala
            -10
                               -5
 Gln Arg Leu Ser Thr Pro Tyr Phe Ser Leu Phe Leu Ser Ile Pro Arg
                       10
                                          15
Cys Ser Phe Pro Arg Arg Ser Ile Asp Arg Thr Cys Ser Ser Xaa Leu
                   25
                                   30
Asp Ser Glu Gly Ser Ser Ser Ile Xaa Pro Ser Thr Pro Phe
                40
                                    45
<210> 1030
<211> 38
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 1030
Met Val Gly Ala Leu Pro Pro Ala Ser Leu Leu Pro Cys Ser Leu Ile
                     -15
                                          -10
Ser Asp Cys Cys Ala Ser Asn Glu Arg Gly Ser Met Gly Val Gly Pro
Ser Glu Pro Arg Arg Gly
           15
<210> 1031
<211> 22
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 1031
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Met Arg Met Thr Lys Asp Pro Leu Gly Ser Leu Ile Ala Ser Leu Ala
 -20
                    -15
                                        -10
 Pro Ser Thr Gly Leu Gly
 <210> 1032
 <211> 57
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
<222> -28..-1
 <400> 1032
Met Lys Leu Gln Phe Ala Phe Cys Tyr Phe Leu Tyr Leu Asp Thr Phe
            -25
                                -20
                                           -15
Phe Leu Phe Leu Phe Phe Xaa Glu Xaa Xaa Xaa Xaa Xaa Xaa Gly
        -10
                        -5
Arg Ser Ala Val Ala Xaa Pro Gln Leu Xaa Ala Ala Ser Thr Phe Xaa
                    10
Phe Gln Ala Ile Phe Leu Pro Gln Xaa
                25
<210> 1033
<211> 84
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -69..-1
<400> 1033
Met Ala Ala Gly Glu Leu Glu Gly Gly Lys Pro Leu Ser Gly Leu Leu
               -65
                                   -60
Asn Ala Leu Ala Gln Asp Thr Phe His Gly Tyr Pro Gly Ile Thr Glu
           ~50
                               -45
Glu Leu Leu Arg Ser Gln Leu Tyr Pro Glu Val Pro Pro Glu Glu Phe
       -35
                           -30
                                               -25
His Pro Phe Leu Ala Lys Met Arg Gly Ile Leu Lys Val Leu Leu Phe
 -20
                       -15
Ser Val Val Ser Gly Leu Glu Gln Asn Pro Leu Ala Ala Gly Phe Arg
Leu Ser His Pro
           .15
<210> 1034
<211> 47
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -31..-1
<400> 1034
Met Met Met Ser Asn Val Met Leu Met Leu Gln Leu Gln Pro Leu Leu
                      -25
Ala Xaa Ser Leu Ile Leu Ser Pro Ser Pro Arg Pro Val Leu Gly Phe
-15
                   -10
                                       -5
Phe Arg Gln Val His Leu Leu Thr Arg Ser His Phe Ser Arg Trp
```

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<210> 1035
<211> 37
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 1035
Met Ile Ile Leu Ile Asn Gln Leu Leu Phe Ile Cys Pro Pro Pro
-20
              -15
                        -10
Pro Ile Ser Ala Ser Ser Asn Tyr His Phe Thr Leu Tyr Leu His Asp
              1
                          5
Ile Asn Phe Phe Ser
 15
<210> 1036
<211> 18
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 1036
Met Thr Asp Val Leu Leu Gln Leu Leu Leu Arg Val Cys Ser Pro Arg
            -10
Thr Arg
<210> 1037
<211> 25
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 1037
Met Gly Leu Phe Leu Cys Cys Ser Leu Leu Ile Phe Cys Leu Val Val
        -10 -5
Leu Ile Ile Thr Glu Leu Gly Tyr Gly
 5
                     10
<210> 1038
<211> 30
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
<400> 1038
Met Gly Ser Trp Ala Leu Thr Trp Leu His Pro Ala Glu Ala Gly Thr
              -10
                  - 5
Arg Val Pro Phe Cys Ser Trp Glu Lys Ser Asp Gly Arg Ser
       5
                        10
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<210> 1039

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<211> 65
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
<400> 1039
Met Met Leu Xaa Xaa Xaa Arg Gly Tyr Pro His Arg Thr Glu Arg Tyr
                           -35
Asp Gly Phe Leu Lys Tyr Ser Asp Pro Asn Asp Ile Ala Leu Ser Val
                        -20
                                            -15
Leu Ser Leu Val Ile Asn Phe Ser Trp Ser Arg Lys Cys Phe Val Pro
                    -5
                                        1
Tyr Tyr Ile Pro Phe Lys Pro Tyr Arg Xaa Pro Tyr Pro Thr Ala Ala
                                15
Arg
<210> 10.40
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -39..-1
<400> 1040
Met Tyr Val Cys Ile Tyr Ile Xaa Leu Xaa Asp Leu Tyr Asp Phe Phe
                -35
                                    -30
                                                        -25
Leu Leu Gly Thr Tyr Phe Phe Glu Arg Lys Cys Phe Val Cys Xaa Leu
           -20
                                -15
                                                    -10
Phe Val Phe Leu Leu Ser Gly Leu Asn Tyr Phe Ser Ile Leu Ser Phe
. - 5
Tyr Pro Arg
10
<210> 1041
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -40..-1
<400> 1041
Met Cys Ile Phe Cys Leu Phe His Leu Leu Tyr His Lys Leu Leu Ser
                                        -30
                   -35
-40
Arg Ser Leu Phe Phe Cys Cys Ile Phe Ser Gly Phe Ile Thr Phe Ile
                -20
                                    -15
Phe Ser Phe Ser Phe Cys Glu Cys Ile Val Gly Met Tyr Ile Tyr Gly
                                1
Ala Arg
    10
<210> 1042
<211> 40
<212> PRT
<213> Homo sapiens
<220>
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<221> SIGNAL

<222> -27..-1

<400> 1042

Met Xaa Ile Cys Tyr Asn Ile Phe Gln Asn Ile Leu Gly Leu Leu Leu -25 -20 -15

Pro Ala Leu Gln Pro Arg Arg Leu 10

<210> 1043

<211> 29

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -26..-1

<400> 1043

Met Ala Ser Ser Met Leu Xaa Ser Phe Gln Thr Phe Met Met Leu Thr
-25 -20 -15

Leu Leu Gly Phe Pro Ser Lys Ala Leu Thr Phe Ile Ser
-10 -5 1

<210> 1044

<211> 33

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -20..-1

<400> 1044

Met Gly Arg Ser Lys Arg Gln Leu Leu Ser Leu Pro Gly Ser Phe Ile
-20 -15 -10 -5

Pro Gly Asn Cys Arg Pro Arg Ile Leu Ser Asn Gly Glu Xaa Arg Arg

1 5 10

Lys

<210> 1045

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -25..-1

<400> 1045

Met Arg Ser Asp Gly Phe Ile Arg Gly Phe Cys Phe Cys Phe Leu
-25 -10 -15

Ile Phe Leu Leu Pro Pro Leu Pro Ala Met Ile Leu Arg Pro Leu Gln -5 5

Pro Cys Gly Ile Ile Ser Pro Ile Lys Pro Leu Phe Pro Phe Phe 10 15 20

<210> 1046

<211> 39

<212> PRT

<213> Homo sapiens

<210> 1050

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<220>
 <221> SIGNAL
 <222> -16..-1
 <400> 1046
 Met Asn Thr Leu Trp Thr Ala Ser Ser Leu Pro Leu Ser Thr His Ser
                        -10
                                     -5
 Gln Arg Thr Met Ile His Trp Asn Val Phe Leu Trp Asn Ser Phe Tyr
                                    10
 Ser Cys Ile Lys Ile Phe Pro
         . 20
 <210> 1047
 <211> 46
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -31..-1
 <400> 1047
Met Thr Trp Thr Lys Cys Pro Leu Pro Leu Gly Pro Ala Phe Phe Thr
                       -25
                                           -20
Gln Cys Cys Leu Ile Gly Leu Leu Val Pro Leu Leu Gly Trp Gly Asn
                   -10
                                       -5
Gln Asn Thr Gln Trp Tyr Pro Thr Ser Lys Met Pro Asp Gly
        5
                                10
<210> 1048
<211> 37
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1
<400> 1048
Met Gly Arg Ser Asn Asp Phe Arg Phe Ala Phe Leu Thr Cys Phe Leu
       -30
                          -25
                                               -20
Gly Trp Glu Ile Val Tyr Phe Leu Val Leu Leu Arg Val Leu Tyr Thr
  -15
                       -10
                                           - 5
Leu Gln Trp Gly Gly
1 .
<210> 1049
<211> 24
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 1049
Met Lys Thr Asp Asn Leu Thr Ser Phe Leu Thr Tyr Met Pro Leu Ile
           -15
Ser Ser Ser Cys Ser Ile Ala Pro
        1
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<211> 130
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
<222> -79..-1
 <400> 1050
 Met Arg Phe Arg Phe Cys Gly Asp Leu Asp Cys Pro Asp Trp Val Leu
                                   -70
                -75
Ala Glu Ile Ser Thr Leu Ala Lys Met Ser Ser Val Lys Leu Arg Leu
          -60
                        . -55
 Leu Cys Ser Gln Val Leu Lys Glu Leu Leu Gly Gln Gly Ile Asp Tyr
                           -40
                                               -35
 Glu Lys Ile Leu Lys Leu Thr Ala Asp Ala Lys Phe Glu Ser Gly Asp
                                        -20
                     -25
 Val Lys Ala Thr Val Ala Val Leu Ser Phe Ile Leu Ser Ser Ala Ala
                            -5
         -10
 Lys His Ser Val Asp Gly Glu Ser Leu Ser Ser Glu Leu Gln Gln Leu
                               10
         5
 Gly Leu Pro Lys Glu His Ala Ala Ser Leu Cys Arg Cys Tyr Glu Glu
                           25
 Lys Gln Ser Pro Leu Gln Lys His Leu Arg Val Cys Ser Leu Arg Met
                        40
 Asn Arg
 50
 <210> 1051
 <211> 79
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -14..-1
 <400> 1051
 Met Phe Leu Ala Ala Leu Phe Thr Val Ala Lys Ile Trp Lys Gln Pro-
                                    -5
                 -10
 Lys Cys Ser Ser Thr Asn Lys Trp Thr Lys Lys Met Trp Tyr Ile Tyr
                           - 10
 Thr Met Glu Tyr Tyr Ser Ala Ile Lys Lys Asp Asp Ile Leu Ser Phe
                        25
 Ala Thr Ile Trp Met Glu Leu Glu Ser Ile Thr Leu Ser Glu Ile Ser
                                       45
                    40
 Gly Xaa Pro Lys Asp Lys Leu Leu Met Phe Ser Leu Ile Cys Gly
                                    60
                55
 <210> 1052
 <211> 30
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -27..-1
 <400> 1052
 Met Glu Ser Ser Thr Phe Ala Leu Val Pro Val Phe Ala His Leu Ser
                            -20
        -25
  Ile Leu Gln Ser Leu Val Pro Ala Ala Gly Ala Xaa Ser Pro
                         ~ 5
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<210> 1053
<211> 84
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -78..-1
<400> 1053
Met Gly Cys Leu Leu Ala Ser Glu Tyr Pro Leu Ser Glu Pro Trp Ala
           -75
                               -70
Pro Gly Pro Phe Thr Gln Tyr Leu Val Asp His His His Thr Leu Leu
                           -55
                                             -50
Cys Asn Gly Tyr Trp Leu Ala Trp Leu Ile His Val Gly Glu Ser Leu
                       -40
Tyr Ala Ile Val Leu Cys Lys His Lys Gly Ile Thr Ser Gly Arg Ala
                -25
                                     -20
Gln Leu Leu Trp Phe Leu Gln Thr Phe Phe Phe Gly Ile Ala Ser Leu
                                   - 5
Xaa Ile Leu Ile
  · 5
<210> 1054
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<400> 1054
Met Cys Cys Trp Ile Trp Val Ala Ser Ile Leu Leu Arg Ile Phe Ala
 -15
                    -10
Ser Val Leu Ile Arg Asp Ile Tyr Leu Trp Phe Ser Phe Phe Phe Phe
                                   10
<210> 1055
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<222> -23..-1
<400> 1055
Met Ile Ser Ser His Leu Tyr Asn Phe Ser Leu Leu Phe Phe Xaa Leu
       -20
                               -15
Trp Leu Arg Tyr Lys Glu Ser Gly Arg Glu Gly Asn Cys Glu Glu Gly
 -5
Ala Phe Ser Arg Trp
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<210> 1056
<211> 122
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<222> -17..-1
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-15

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 Met Gly Trp Gln Arg Leu Leu Leu Pro Arg Pro Pro Ala Ser Thr
       . -15
                            -10
                                                 -5
 Gly Ala Ser Asn Ala Thr Arg Xaa Pro Lys Xaa Leu Tyr Arg Xaa Tyr
                                         10
Asn His Gly Val Leu Lys Ile Thr Ile Cys Lys Ser Cys Gln Lys Pro
                 20
                                     25
 Val Asp Lys Tyr Ile Glu Tyr Asp Pro Val Ile Ile Leu Xaa Asn Ala
             35
                                 40
 Ile Leu Cys Lys Ala Xaa Ala Tyr Arg His Ile Leu Phe Asn Thr Gln
         50
                                                 60
 Ile Asn Asn Lys Leu Pro Ile Leu Leu Ala Phe Leu Pro Ser Cys Gly
                                             75
 Xaa Thr Ala His Asp Gly Lys Lys Lys Pro Asn Phe Ile Leu Leu Leu
                     85
                                         90
Lys Xaa Tyr Tyr Tyr Leu Ala Thr Glu Asn
                 100
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<222> -19..-1
<400> 1057
Met Ala Ala Gly Val Ser Leu Leu Ala Leu Val Val Arg Val Ile Leu
                -15
                                    -10
Ser Thr Ala Ile Leu Cys Pro Ser Gly Ala Ser Arg Arg Gln Arg Ser
                                                10:
Ser Glu Val Glu Trp Gly Thr Asp Ser
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<210> 1058
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<400> 1058
Met Asn Pro Leu Phe Trp Leu Ile Leu Cys Ser Gly Leu Leu Cys Asn
-15
                   -10
Lys Ser Phe
<210> 1059
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<213> Homo sapiens
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<221> SIGNAL
<222> -18..-1
<400> 1059
Met Arg Gly Ala Trp Ile Ser Ile Phe Leu Ser Ser Leu Ser Leu Ser
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Leu Ser Leu Phe
<210> 1060
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<400> 1060
Met Ser Gln Lys Arg Leu Asp Phe Ile Tyr Gln Leu Phe Val Leu Leu
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                           -15 -10
Pro His Phe Phe Leu Ser Phe Leu Ser Pro Phe Tyr Leu His Pro Trp
                               1
<210> 1061
<211> 52
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<400> 1061
Met Tyr Leu Tyr Leu Leu Ser Ile Cys Met Ser Ser Leu Lys Lys Cys
           -30
                               -25
                                                   -20
Leu Phe Lys Phe Leu Ala His Phe Leu Ile Gly Leu Thr Val Cys Phe
       -15
                           -10
                                               -5
Gly Glu Gly Xaa Leu Met Ser Tyr Arg Ser Ser Tyr Leu Leu Lys
                                       10
Gly Pro Pro Gly
<210> 1062
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<221> SIGNAL
<222> -22..-1
<400> 1062
Met Gly Phe Trp Cys Glu Cys Pro Phe Cys Leu Leu Val Phe Leu Leu
                           -15
Thr Glu Trp Thr Ser Ser Lys Leu Gln Lys Thr
                       1
   -5
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<211> 24
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<222> -22..-1
<400> 1063
Met Trp Trp Gly Arg Cys Phe Ile Arg Val Leu His Leu Phe Pro Leu
       -20
                           -15
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Thr Pro Ala Ser Thr Gly His Trp
    -5
<210> 1064
 <211> 58
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<400> 1064
Met Arg Asp Pro Leu Ala Asp Met Val His Ser Tyr Leu Ser Ser Ser
                -25.
                                   -20
Leu Phe Met Ala Leu Pro Pro Val Leu Ser Ser His Gly Ser Arg Asn
                -5
            -10
Leu Arg Ile Trp Gly Ser Pro Phe Gly Gly Ala Leu Thr Lys Gly Lys
                        10
Ala Pro Pro Thr Pro Ala Gln Pro Ala Leu
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Met Ser Ser Ala Trp Leu Cys Leu Pro Cys Ser Leu Cys Val Ser Gln
                     -10
Leu Leu Pro Ser Tyr Ser Leu Leu Ile Pro Ala Pro
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   1
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Met Ser Pro Met Trp Ala Gly Leu Leu Ser Leu Leu Gly Pro Leu Xaa
                     -15
Pro Pro Met Arg Ala Cys Ser Val Cys Val Leu
                   1
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Met Ser Leu Asn Glu Leu Ser Ile Ala Asp Leu Leu Pro Ser Ser Ser

```
-15
                                 -10
Phe Ala Asn Pro Lys Leu Ser Gly Pro Ile Ser Ile Ser Val Thr Ser
                                             10
Ala Gly Ser Pro Pro Gly Ala
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<400> 1068
Met Lys Asp Leu Leu Gly Thr Ala Phe Leu Glu Gly Ser Leu Ala Ala
                  . -10
Tyr Leu Thr Met Ala Asn Ile Thr His Val
<210> 1069
<211> 29
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<213> Homo sapiens
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<221> SIGNAL
<222> -19..-1
<400> 1069
Met Ala Asn Asp Ile Lys His Leu Phe Met Cys Leu Leu Thr Ile Cys
                -15
                                    -10
Ile Ser Ser Leu Glu Lys Leu Pro Phe Phe Phe Phe
                           5
<210> 1070
<211> 98
<212> PRT
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<222> -24...-1
<400> 1070
Met Tyr Gln Lys Val Thr Ser Tyr Cys Arg Ser Ala Thr Leu Val Gly
                -20
                                    -15
Phe Thr Val Gly Ser Val Leu Gly Gln Ile Leu Val Ser Val Ala Gly
            - 5
Trp Ser Leu Phe Ser Leu Asn Val Ile Ser Leu Thr Cys Val Ser Val
                                            20
Ala Phe Ala Val Ala Trp Phe Leu Pro Met Pro Gln Lys Ser Leu Phe
                    30
Phe His His Ile Pro Ser Thr Cys Gln Arg Val Asn Gly Ile Lys Val
                                   50
Gln Asn Gly Gly Ile Val Thr Asp Thr Gln Leu Leu Thr Pro Ser Trp
                                65
Leu Gly
<210> 1071
<211> 19
<212> PRT
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<213> Homo sapiens
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 <222> -17..-1
 <400> 1071
 Met Met Pro Pro Ala Leu Phe Phe Leu Leu Arg Ile Ala Trp Leu Leu
  -15
                             -10
                                                 -5
 Gly Leu Phe
    1
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<211> 38
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<221> SIGNAL
<222> -21..-1
<400> 1072
Met Asn Cys Val Thr Leu Ile Gln Ala Leu Ser Leu Trp Ala Ser Val
    -20
                        -15
                                            -10
Ser Pro Ser Trp Met Cys Arg Pro Pro Ala Ser Phe Ile Ile Thr Thr
Thr Thr Thr Cys Gly
<210> 1073
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<400> 1073
Met Leu Ser Leu Leu Ser Leu Met Ala Arg Thr Asp Leu Val Phe Cys
  -15
                     -10
Ser Pro Arg
<210> 1074
<211> 255
<212> PRT
<213> Homo sapiens
·<220>
<221> SIGNAL
<222> -34..-1
<400> 1074
Met Val Gly Glu Ala Gly Arg Asp Leu Arg Arg Arg Arg Ala Val Ala
               -30
                                    -25
                                                        -20
Val Thr Ala Glu Lys Met Ala Val Leu Ala Pro Leu Ile Ala Leu Val
           -15
                                -10
Tyr Ser Val Pro Arg Leu Ser Arg Trp Leu Ala Gln Pro Tyr Tyr Leu
       1
                       5
Leu Ser Ala Leu Leu Ser Ala Ala Phe Leu Leu Val Arg Lys Leu Pro
                   20
Pro Leu Cys His Gly Leu Pro Thr Gln Arg Glu Asp Gly Asn Pro Cys
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515 40 Asp Phe Asp Trp Arg Glu Val Glu Ile Leu Met Phe Leu Ser Ala Ile 55 Val Met Met Lys Asn Arg Arg Ser Ile Thr Val Glu Gln His Ile Gly 70 Asn Ile Phe Met Phe Ser Lys Val Ala Asn Thr Ile Leu Phe Phe Arg 85 Leu Asp Ile Arg Met Gly Leu Leu Tyr Ile Thr Leu Cys Ile Val Phe 100 105 Leu Met Thr Cys Lys Pro Pro Leu Tyr Met Gly Pro Glu Tyr Ile Xaa 120 · Tyr Phe Asn Asp Lys Thr Ile Asp Glu Glu Leu Glu Arg Asp Lys Arg 130 135 Val Thr Trp Ile Val Glu Phe Phe Ala Xaa Trp Ser Asn Asp Cys Gln 150 Ser Phe Ala Pro Ile Tyr Ala Asp Leu Ser Leu Lys Tyr Asn Cys Thr 165 170 Gly Leu Asn Phe Gly Lys Val Asp Val Gly Arg Tyr Thr Asp Val Ser 180 185 Thr Arg Tyr Lys Val Ser Thr Ser Pro Leu Thr Lys Gln Leu Pro Thr 195 200 Leu Ile Leu Phe Gln Gly Gly Lys Glu Ala Met Arg Arg Pro Gln 215 <210> 1075 <211> 153 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -17..-1 <400> 1075 Met Thr Met Tyr Leu Trp Leu Lys Leu Leu Ala Phe Gly Phe Ala Phe -10 - 5 Leu Asp Thr Glu Val Phe Val Thr Gly Gln Ser Pro Thr Pro Ser Pro 10 Thr Gly Leu Thr Thr Ala Lys Met Pro Ser Val Pro Leu Ser Ser Asp Pro Leu Pro Thr His Thr Thr Ala Phe Ser Pro Ala Ser Thr Phe Glu

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<220>
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<222> -17..-1

-45

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 Met Thr Met Tyr Leu Trp Leu Lys Leu Leu Ala Phe Gly Phe Ala Phe
       - 15
              -10
                                             - 5
 Leu Asp Thr Glu Val Phe Val Thr Gly Gln Ser Pro Thr Pro Ser Pro
                                        10
 Thr Gly Val Ser Ser Val Gln Thr Pro Gln
                 20
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 Met Thr Met Tyr Leu Trp Leu Lys Leu Leu Ala Phe Gly Phe Ala Phe
        -15
                            -10
                                        -5
 Leu Asp Thr Glu Val Phe Val Thr Gly Gln Ser Pro Thr Pro Ser Pro
                                       10
 Thr Gly Val Ser Ser Val Gln Thr Pro His Leu Pro Thr His Ala Asp
                20
                                   25
Ser Gln Thr Pro Ser Ala Gly Thr Asp Thr Gln Thr Phe Ser Gly Ser
           35
                               40
Ala Xaa Met Gln Asn Ser Thr Leu Pro Gln Ala Ala Met Leu Ser Gln
     50
                            55
Met Ser Gln Glu Arg Gly Val
    65
<210> 1078
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<222> -36..-1
<400> 1078
Met Arg Gly Ala Thr Trp Pro Trp Pro Cys Leu Pro Ala Arg Thr Ser
                       -30
                                           -25
Thr Ala Ala Ser Ile Ala Arg Leu Phe Leu Leu Ser Gly Thr Ile Trp
                   -15
                                       -10
Ile Ala Ile Cys Lys Pro Thr Thr Asn Gly
<210> 1079
<211> 72
<212> PRT
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<221> SIGNAL
<222> -64..-1
Met Gly Val Leu Pro Asp Leu Val Val Glu Ile Phe Gly Val Asn Lys
               -60
                                -55
Cys Arg Leu Ser Trp Gly Leu Val Leu Glu Ser Leu Gln Gln Pro Leu
```

-40

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Ile Asn Arg His Leu Ile Tyr Cys Leu Gly Asp Ile Ile Leu Xaa Xaa
     -30
                            -25
                                           -20
Leu Asp Leu Ser Ala Leu Leu Arg Ser Leu Leu Pro Xaa Leu Xaa
                        -10
   -15
Gln Ile Pro Gln Ala Thr Leu Arg
<210> 1080
<211> 42
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<222> -15..-1
<400> 1080
Met Thr Ala Leu Gly Phe Val Leu Leu Ala Pro Arg Gly Trp Gly Ser
                    -10
                                       -5
Leu Thr Val Met Val Glu Gly Lys Glu Glu Gln Val Thr Ser Tyr Thr.
           5 .
                              10
Asp Gly Ser Arg Gln Arg Asp Ser Asn Phe
        20
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<210> 1081
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<400> 1081
Met Lys Arg Ile Arg Arg Lys Arg Arg Asn Glu Val Thr Ile Gln Pro
               -35
                                  -,30
Phe Pro Ile Arg Leu Pro Leu Leu Pro Pro Leu Ile Ser Phe Leu His
           -20
                               -15
Thr Leu Gln Val Val Cys Ser Val Ile Met Lys Ser Ile Arg Lys Ala
Phe Val Leu Cys Gly Phe Leu Tyr Phe Glu Phe Phe Asp Gln Lys Leu
                   15
                                       20
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<211> 59
<212> PRT
<213> Homo sapiens
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<222> -22..-1
<400> 1082
Met Leu Pro Leu His Cys Phe Phe Xaa Val Xaa Leu Phe Xaa Xaa
       -20
                           -15
Val Xaa Val Xaa Xaa Ala Ala Leu Leu Arg Tyr Asn Xaa Ser Ile Gln
Xaa Gly Arg Ala Gln Xaa Leu Xaa Pro Xaa Ile Pro Xaa Leu Trp Glu
              15
                                  20
Thr Lys Xaa Gly Arg Leu Leu Glu Pro Arg Asn
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 <213> Homo sapiens
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 <222> -21..-1
 <400> 1083
 Met Val Ser Val Phe Arg Ser Glu Glu Met Cys Leu Ser Gln Leu Phe
   -20
                        -15
 Leu Gln Val Glu Ala Ala Tyr Cys Cys Val Ala Glu Leu Gly
 <210> 1084
 <211> 41
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 <222> -28..-1
<400> 1084
Met Ala Ala Leu Arg Ser Thr Leu Thr Trp Thr Glu Val Val Gly Trp
            -25
                               -20
                                                    -15
Trp Ser Val Ala Ser Leu Leu Ser Asp Val Ala Ala Trp Trp Pro Pro
 -10
                           -5
His Ser Thr Ser Thr Arg Gly Gly Val
                    10
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<211> 47
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<400> 1085
Met Asn Ala Leu Val Asp Gly Lys Arg Leu Xaa Xaa Cys Ile Arg Tyr
                -40
                                   -35
                                                       -30
Phe Asp Ser Ile Ser Leu Tyr Ser Lys Ala Ser Leu Ser Cys Cys Leu
           -25
                               -20
                                                   ~15
Val Cys Val Phe Thr Cys Ser Leu Leu Ala Phe Phe Ser Pro Cys
       -10
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<400> 1086
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Leu Lys Gly
               -15
                                   -10
Val Gln Cys Glu Leu Gln Val Val Glu Ser Gly Gly Gly Leu Val Gln
Pro Gly Arg Ser Leu Arg Leu Ser Cys Arg Thr Ser Gly Phe Ala Phe
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20
 Asp Asp Tyr Asn Leu Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
                    35
                                       40
                                                             45
 Glu Trp Val Gly Phe Ile Arg Ser Lys Pro Tyr Gly Glu Thr Thr
                                     55
 Tyr Ala Ala Trp
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 <222> -14..-1
 <400> 1087
Met Ser Leu Phe Xaa Leu Xaa Xaa Leu Arg Gln Ser Phe Thr Xaa Xaa
                -10
                                    - 5
Ala Gln Ala
    5
<210> 1088
<211> 30
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<221> SIGNAL
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<400> 1088
Met Ile Ser Ala His Cys Ser Phe Tyr Phe Leu Ala Ser Ser Ser Leu
               ~15
                                  -10
Ser Thr Ser Ala Ser Xaa Arg Thr Gly Ile Thr Asp Val Ser
                            5
<210> 1089
<211> 43
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<213> Homo sapiens
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<221> SIGNAL
<222> -24..-1
<400> 1089
Met Asn Ala Glu Asn Asn Phe Phe Gly Phe Val Cys Leu Phe Val Phe
               -20
                                   - 15
Leu Tyr Thr Thr Pro Cys Asn Cys Phe Gly Leu Glu His Leu Trp Ile
        -5
                               1
Leu Ser Phe Met Val Val Leu Gly Xaa Thr Arg
  10 .
                       15
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<221> SIGNAL <222> -15..-1

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 Met Thr Met Ala Val Gly Ala Ala Xaa Xaa Leu Pro Cys Cys His
            -20
                                -15
                                                    -10
 Leu Leu Thr Cys Val Ser Ser Leu Arg Xaa Asp Ile Tyr Pro His
<210> 1091
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 <222> -25..-1
<400> 1091
Met Arg Arg Lys Arg Arg Glu Arg Lys Glu Arg Lys Ser Ile Leu Leu
                    -20
                                    -15
Ala Ala Leu Ser Arg Asn Ile Ser Pro Gly Gln Thr Tyr Arg Thr Ser
Pro Ala
<210> 1092
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<222> -23..-1
<400> 1092
Met Gly Ser Pro Tyr Val Ala His Val Gly Leu Glu Leu Leu Thr Ser
                 -15
           -20
Ser Asp Pro Pro Ser Leu Ala Ser Gln Val Leu Gly Ile His
       - 5
                           1
<210> 1093
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<222> -19..-1
<400> 1093
Met His Leu Tyr Thr His Val Cys Trp Leu Thr Leu Thr Leu Ala His
               -15
                                  -10
Ser His Ser Leu Thr His Thr His Thr Leu Thr Pro Ser His Thr Arg
                           5
Thr His Ser His Thr Cys Ala Cys Leu His Ala His Lys
 15
                       20
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<211> 51
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 Met Arg Leu Ser Leu Thr Phe Tyr His Phe Pro Leu Cys Trp Gly His
                      -10
                                          -5
 Gln Ala Val Pro Thr Trp Trp Xaa Xaa Ile Ile Gln Pro Cys His Cys
                                  10
 Ala Leu Cys Thr Ser Ala Glu Gly Val Gln Ser His Ile Ile Ser Xaa
         20
                              25
 Ile Tyr Arg
     35
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 <400> 1095
 Met Asn Val Leu Ile Ile Val Phe Val Ala Phe Ala Phe Gly Phe Leu
                 -10
                                     - 5
 Val Met Lys Ser Leu Leu Lys Pro Met Ser Arg Arg Val Phe Leu Met
Leu Ser Ser Arg Ile Phe Met Val Ser Gly Leu Arg Phe Lys Ser Leu
Ile His Leu Glu Leu Ile Phe Val Tyr Lys Leu Arg Asp Glu Asp Pro
                                         45
Val Ser Phe Phe Tyr Met Trp Leu Ala Asn Tyr Pro Ser Thr Ile Cys
                 55
                                     60
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<400> 1096
Met Ser Arg Arg Ser Met Leu Leu Ala Trp Ala Leu Pro Ser Leu Leu
                    -15
                                    -10
Arg Leu Gly Ala Ala Gln Glu Thr Glu Asp Pro Ala Cys Cys Ser Pro
Ile Val Pro Arg Asn Glu Trp Lys Ala Leu Ala Ser Glu Cys Ala Gln
        15
                            20
His Leu Ser Leu Pro Leu Arg Tyr Val Val Val Ser His Thr Ala Gly
                        35
Ser Ser Cys Asn Thr Xaa Ala Ser Cys Gln Gln Gln Ala Arg Asn Val
                    50
Gln His Tyr His Met Lys Thr Leu Gly Trp Cys Asp Val Gly Tyr Asn
                65
                                    70
Xaa Leu Asp Trp Arg Arg Ala Arg Ile Xaa Gly Pro Trp Xaa Glu
           80
                                85
Leu His Gly Xaa
       95
<210> 1097
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<221> SIGNAL
<222> -14..-1
<400> 1097
Met Val Phe Leu Phe Leu Met Ile Ser Val Phe Ala Gly Cys Gln Ile '
              -10
                                 -5
Pro Ser Gly
 5
<210> 1098
<211> 38
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<222> -21..-1
<400> 1098
Met Gly Ser Arg Pro Val Ser Xaa Ala Gly Leu Glu Leu Leu Ala Ser
                  -15
 -20
                                  -10
Ser Asn Ser Ser Ala Leu Pro Phe Gln Cys Ser Gly Ile Thr Gly Met
                          . 5
              1
Ser Xaa His Thr Leu Ala
        15
<210> 1099
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<221> SIGNAL
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<400> 1099
Met Leu Cys His Leu Ser Leu Val Phe Leu Gly Xaa Gly Gln Phe Trp
 -10 -5
Ser Gln Asn
 5
<210> 1100
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<212> PRT
<213> Homo sapiens
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<222> -17..-1
<400> 1100
Met Thr Asn Leu Phe Met Cys Leu Phe Ala Ile Cys Ile Ser Ser Asn
 -15 -10
Ala Lys Cys Leu Phe Ser Leu Phe Pro Phe Phe Ile Glu Gly
                                   10 -
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<212> PRT
<213> Homo sapiens
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 <222> -27..-1
 <400> 1101
 Met Leu Gly Tyr Ile Trp Xaa Gln Asp Lys Val Phe Ala Asn Cys Val
         -25
                             -20
 Leu Phe Thr Leu Leu Val Ser Thr Arg Ser Gly Arg Ser Arg Ala Gly
                         ~5
 Cys Ala Trp Arg Trp Arg Gly Arg Trp Ser Val Gly Gln Lys Gly Xaa
                 10
                                     15
 <210> 1102
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 <222> -15..-1
 <400> 1102
 Met Xaa Leu Ile Leu Ser Leu Gln Val Cys Arg Pro Ala Thr Leu Asp
             -10
                                        - 5
Gln Ala Thr Arg Ala Thr Thr Pro Cys Arg Leu Arg
<210> 1103
<211> 41
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<213> Homo sapiens
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<221> SIGNAL
<222> -37..-1
<400> 1103
Met Cys His Arg Arg Trp Leu His Leu Ser Thr Arg His Leu Gly Phe
        -35
                            ~30
                                               -25
Lys Pro Arg Ile His Tyr Val Phe Val Leu Met Leu Ser Leu Pro Leu
  -20
                        -15
Pro Pro Thr Pro Gln Gln Ala Leu Gly
                    1
<210> 1104
<211> 36
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -19..-1
<400> 1104
Met Asp His Val Val Ile Phe Val Ile Phe Pro Ala Ala Leu Leu Leu
               -15
                                  -10
Cys Trp Gly Gly Leu Ile Pro Leu Cys Ile Ile Tyr Pro Pro Ile Ala
                                               10
Asp Thr Val Gly
  15
<210> 1105
<211> 30
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<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -25..-1
<400> 1105
Met Leu Thr Asn Leu Phe Phe Gln Val Ala His Pro Leu Ile Ile Ile
             -20
                                        -15
Leu Xaa Phe Asp Ile Tyr Ser Leu Ala Phe Ile His Asp Val
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Met Leu Phe Gly Leu Arg Gly Met Leu Pro Leu Thr Gln Gln Ala Pro
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Ile Pro His Leu Arg Cys Lys Leu Ser Val Thr
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Met Arg Val Cys Met Arg Leu Cys Ala Cys Val Tyr Ala Cys Val Cys
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Ala Ser Val Ser Ala Cys Val Tyr Xaa Cys Val Cys Met Xaa Val Arg
- 5
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Ala His Leu Cys Val Cys Met Cys Val Cys Met Cys Val His Leu Cys
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Val Cys Met Cys Val Cys Val Cys Ala Ser Val Cys Val Cys Met Cys
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Ala Cys Val Cys Met Cys Val Cys Val Arg Ala Ser Val Cys Val
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Met Val Ile Thr Ser Asn Ser Tyr Leu Ile Ala Asn Leu Val Leu Phe
                       -15
Ile Ser Ile Ala Ala Leu Arg
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Met Glu Glu Leu Asp Arg Lys Trp Arg Glu Lys Val Leu Pro Ala Ala
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Lys Leu Ile Lys Arg Arg Asn Leu Phe Ser Thr Cys Thr Pro Gln Tyr
                    -30
                                        -25
-35
                                                            -20
Gly Thr His Ala Ala Phe Leu Ser Leu His Ala Ser Leu Val Thr Lys
                -15
Ala Phe Ser Ile Asn Ser Trp Glu Trp
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Met Val Ser Gly Ala Gln Ala Pro Ser Ser Gln Arg Pro Leu Leu
-25
                    -20
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Cys Pro Leu Ser Ser Gly Ser Pro Cys Pro Arg
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Met Ser Cys Leu Leu Arg Ala Tyr Ile Ile Trp Ile Phe Pro Ser Phe
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                                                -15
Leu Pro Ser Leu Leu Ser Ser Phe Leu Leu Ser Leu Pro Pro Ser Gly
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<400> 1112
Met Phe Gln Leu Leu Ile Leu Cys Gln Met Asn Ser Leu Lys Ile Phe
                       -30
                                            -25
Ser Pro Ile Leu Gly Trp Ser Leu His Phe Val Tyr Cys Phe Leu Cys
```

```
-20
                    -15
                                        -10
Cys Ala Glu Ala Phe Leu Leu Asp Met Ile Pro Phe Met Gln Phe Tyr
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                                5
Phe Gly Tyr Leu Cys Leu Trp Gly Ile Thr Leu Lys Ile Phe Ala Gln
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Ser Asn Trp
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Met Ala Leu Leu Gly Lys Arg Cys Asp Val Pro Thr Asn Gly Cys Gly
         -45
                                -40
                                                   -35
Pro Asp Arg Xaa Xaa Xaa Gly Xaa Asn Pro Gln Xaa Arg Asp His His
       -30
                           -25
                                               -20
Gln Xaa Xaa Val Cys Leu Arg Leu His Val Leu Ser Ala Val Gln Thr
  -15
                       -10
Glu Arg Arg Gly Asp Gly
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<400> 1114
Met Arg Pro Ala Leu Arg Ser Phe Trp His Ser Ser Gly Gly Pro Pro
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                           -25
                                               -20
Pro Ser Ala Thr Leu Ala Leu Leu Ser Ser Asp Ser Val Ala Thr Gly
  -15
                       -10
Ser Val Val Ser Arg
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<400> 1115
Met Leu Cys Ala Cys Lys Ala Arg Gly Val Met Leu Leu Leu Phe Ser
                       -20
                                           -15
Gly Trp Leu Val Trp Trp Gly Ser Arg Ser Ser Gln Xaa Leu Arg Met
Pro Glu Xaa Xaa Val Ser Gly Glu Gly Arg Ser Asp Xaa Xaa Pro His
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Gly
<210> 1116
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 Met Ile Ser Ser Leu Ser Gly Arg Val Pro Val Ile Leu Gly Asn
        -40
                            -35
                                        -30
 Leu Met Gly Val Gly Ala Ala Val Arg Arg Met Gly Phe Ser Leu Ile
  -25
                        -20
                                            -15
 Leu Pro Thr Ser Pro Ser Pro Ala His Ser Gly Ser Ala Pro Ser Ala
 -10
                    -5
                                        1
Gly Pro Arg
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Met Gly Ile Ile Gln Xaa Ile Leu Ala Thr Ser Arg Asp Cys Tyr Ser
                        -40
                                           -35
Phe Lys Lys Pro Ile Pro Lys Lys Pro Thr Met Leu Ala Leu Ala
-30
                   -25
                                       -20
Lys Ile Leu Leu Ile Ser Thr Leu Phe Tyr Ser Leu Leu Ser Gly Ser
               -10
                                    - 5
His Gly Lys Xaa Asn Gln Asp Val
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Met Met Leu Ser Thr Phe Ser Tyr Ala Cys Leu Pro Phe Val Cys Leu
           -20
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Leu Leu Arg Asn Val Tyr Ser Asp Leu Leu Pro Asn Arg
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<221> SIGNAL
<222> -24..-1
<400> 1119
Met Leu Ala Ile Leu Thr Gly Gly Arg Trp Tyr Leu Ile Val Val Leu
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-20

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528
Val Cys Ile Ser Leu Val Ile Ile Asp Asp Asp Glu His Gly
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<212> PRT
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Met Leu Pro Leu Gly Leu Lys Val Leu Gly Leu Gln Ala Arg Gly
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Thr Thr
<210> 1121
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<222> -28..-1
<400> 1121
Met Arg Pro Thr Met Glu Phe His Ser Val Leu Cys Gly Val Thr Pro
            -25
                                -20
                                                    -15
Thr Leu Leu Val Met Trp Leu Ser Pro Gln Met Ala Ser Ser Pro Ser
       -10
                            -5
                                                1
Gln Ala Pro Gly Met Glu Pro Cys Ala Ser Gly Ile Ser Gln Arg Ala
                    10
                                        15
<210> 1122
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<213> Homo sapiens
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<222> -33..-1
<400> 1122
Met Gly Lys Lys Ile Trp Thr Pro Ser Ser Tyr Pro Met Pro Ser
           -30
                               -25
His Lys His Val Ser Leu Cys Leu Leu Thr Val Ala Val Leu Val Leu
       -15
                            -10
Thr Phe Lys Ser Leu Ile His Phe Glu Xaa Ile Phe Ala Tyr Glu Ile
Gly Val Gln Gly
<210> 1123
<211> 31 -
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 1123
Met Ser Pro Val Leu Cys Phe His Arg Cys Ser Cys Pro Ser Leu Leu
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-20
                                 -15
Ser Pro Ile Ser Pro Ser Gln Ala Cys Pro Glu Pro Leu Leu Gly
                             1
<210> 1124
<211> 34
<212> PRT
<213> Homo sapiens
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Met Leu Gln Leu Ser Phe Ser Val Phe Ile Leu Ile Met Phe Val Cys
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Met Cys Val Cys Val Cys Val Tyr Arg Leu Phe Ser Ser Ser
                             1
Ser Pro
 10
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<400> 1125
Met Lys Ser Thr Val Ser Ser Arg Glu Val Ala Thr Val Asp Lys Met
   -90
                      -85
Lys Arg Arg His Ala Glu Tyr Cys Ala Gln Gly Leu Gln Arg Phe Lys
                - -70
                                    -65
Ala Gln Leu Ser Gln Asp Thr Leu Pro Xaa His Pro His Leu Glu Xaa
              -55
                                -50
Glu Lys Gly Leu Glu Gly Leu Glu Asn Val Pro Leu Lys Gly Glu
          -40
                            -35
Lys Pro Gly Glu Gly Pro Glu Ser Pro Lys Lys Arg Arg Arg Val
                       -20
                                          -15
Leu Leu Gly Ala Gly Ile Pro Pro Val Ser Ser Ala Pro Arg Arg Gln
 -10
                   -5
Ser Gln Gln Ala Thr
              10
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<211> 36
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
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<400> 1126
Met His Asn Ser Cys Arg Pro Val His Leu Phe Phe Phe Phe Phe Xaa
              -15 -10
Glu Thr Gly Ser Arg Ser Asn Xaa Trp Leu Glu Xaa Ser Gly Ala Ile
                          5
Ile Ala Asn Ser
       15
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<400> 1130

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<210> 1127
<211> 44
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<213> Homo sapiens
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<400> 1127
Met Glu Ala Tyr Leu Asn Asp Ser Leu Leu Thr Pro Ser Asp Ser Pro
     -40
                     -35
                                                -30
Asp Phe Glu Ser Val Gln Ala Gly Pro Xaa Ala Arg Pro Thr Phe Arg
                        -20
                                           -15
Leu Tyr Leu Ser Leu Pro Val Ser Gln Ala Gly Pro
-10
                    -5
<210> 1128
<211> 70
<212> PRT
<213> Homo sapiens
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<400> 1128
Met Pro Ala Leu Gly Pro Ala Leu Leu Gln Gly Ser Leu Xaa Arg Val
               -10
                                    - 5
Gly Pro His Pro Pro Ala Pro Ser Thr Asn Cys Ile His Ser Gln Trp
       5
                           10
                                               15
His Val Ser Ala Ala Xaa Gly Lys Gly Pro His Leu Arg His Pro Leu
                       25
                                           30
Xaa Gly Xaa Tyr Gln Leu Pro Val Pro Ala Glu Pro Trp Ala Ala Ala
                   40
                                       45
Gly Gly His Ser Val His
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Met Val Gly Ile Leu Pro Leu Cys Cys Ser Gly Cys Val Pro Ser Leu
               -15
                                   -10
Cys Cys Ser Ser Tyr
<210> 1130
<211> 22
<212> PRT
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<221> SIGNAL
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Met Ala His Ser Ile Leu Leu Leu Ala Ser Gln Ala Gly Cys Leu Arg
                  -10
                                      -5
   Ser Phe Leu Gly Asn Trp
          5
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   <212> PRT
   <213> Homo sapiens
   <220>
   <221> SIGNAL
   <222> -20..-1
   <400> 1131
   Met Thr Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Phe Lys
                      -15
                                          -10
   Gly Val His Cys Glu Gly Xaa Ile Gly Gly Val Gly Gly Ala
                                  5
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  <212> PRT
  <213> Homo sapiens
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  <221> SIGNAL
  <222> -14..-1
  <400> 1132
  Met Asn Thr Val Phe Leu Leu Phe Phe Gly Cys Phe Phe Phe Glu
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  <210> 1133
  <211> 47
  <212> PRT
. <213> Homo sapiens
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 <222> -24..-1
  <400> 1133
  Met Trp Ala Ser Ser Pro Trp Pro Ser Ala Trp Ser Cys Cys Leu
                  -20
                                     -15
                                            -10
  Ser Ser Ser Phe Ile Ala Gly Arg Arg Arg Gly Trp Thr Gln Met
          - 5
                                 1
  Trp Leu Thr Arg Pro Phe Ser Pro Gln Ala Ser Ser Pro Ser Ala
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  <222> -33..-1
  <400> 1134
  Met Thr Met Pro Ile Ser Ser Tyr Ser Gln Asn Val Leu Ser Asn Phe
                                 -25
 . His Asp Gly Tyr Phe Met Leu Ile Ile Leu Ser Ala Ile Leu Leu Asn
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-10
 Ser Phe Ile Gly Cys Val Ser Phe Tyr His Cys Phe Ser Trp Gly Ser
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                                     10
 Gly
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 Met Leu Thr His Gly Ala Ser Leu Ser Leu Val Ile Phe Leu Leu Thr
-20 -15 -10
 Val Lys His Cys Phe Arg Tyr Arg Val Tyr Lys Thr
           1
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<222> -22..-1
<400> 1136
Met Ser Ser Val Glu Thr Asp Trp Gly Phe Trp Thr Ser Ile Pro Ile
                   -15
                                         -10
Leu Pro Leu Ser Ser Gly Arg Gln Leu Pro Leu Pro Thr Arg Glu Trp
 -5
Gly Met Trp
<210> 1137
<211> 82
<212> PRT
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<400> 1137
Met Phe Ala Ser Pro Arg Arg Trp Ser Ser Xaa Lys Ala Phe Ser Gly
        -30
                             -25
Gln Arg Thr Leu Leu Ser Ala Ile Leu Ser Met Leu Ser Leu Ser Phe
 -15
             -10
Ser Thr Thr Ser Leu Leu Ser Asn Tyr Trp Phe Val Gly Thr Gln Lys
                 5
                                    10
Val Pro Lys Pro Leu Cys Glu Lys Gly Leu Ala Ala Lys Cys Phe Asp
             20
                               25
Met Pro Val Ser Leu Asp Gly Asp Thr Asn Thr Ser Thr Gln Glu Val
Val Xaa
<210> 1138
<211> 63
<212> PRT
<213> Homo sapiens
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<400> 1141

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 <222> -16..-1
 <400> 1138
 Met Pro Ile His Ser Val Phe Leu Cys Ala Pro Ala Leu Val Phe Pro
   -15
                         -10
 Arg Pro Val Ala Trp Lys Ala Glu Arg Pro Ser Leu Cys Phe Gly Ala
 1
                                     10
 Ser Leu Pro Pro Leu Gly Arg Ser Leu Leu Gly Gln Gly Ser Ser Phe
      - 20
 Ile Ser Trp Gly Thr Gln Ala Ala Ile Val Glu Leu Xaa Pro His
      35
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 <211> 80
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
 <222> -62..-1
 <400> 1139
 Met Val Tyr Asp Glu Lys Ser Leu Ser Cys Ser His Thr Pro Ala Thr
        -60
                             -55
 Gln Phe Leu Ser Trp Asp Ala Ser Ser Val Tyr Ser Phe Leu Tyr Ile
                         -40
                                             -35
 Leu Ser Ala Arg Val Asn Val Asp Val Xaa Xaa Tyr Ile Arg Val Tyr
                     -25
                                         -20
                                                             -15
 Ile Leu Ala Cys Val Phe Phe Leu Ser His Pro Leu Phe Xaa Xaa Pro
               -10
                                     - 5
 Asn Gly Ser Val Tyr Cys Xaa Arg His Ser Pro Pro Tyr Leu Phe Cys
                             10
                                                 15
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 <222> -36..-1
<400> 1140
 Met Leu Pro Leu Ser Pro Thr Lys Phe Leu Asn Val Phe Leu Gly Leu
                     . -30
                                       -25
 Phe Leu Tyr Tyr Leu Gln Leu Val Cys Leu Leu Ile Ile Ser Leu Val
                    -15
                                        -10
 Leu Ile Ser Gly Leu Gly
 <210> 1141
 <211> 48
 <212> PRT
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 <221> SIGNAL
 <222> -29..-1
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Met Asp Lys Val Glu Leu Pro Pro Pro Asp Leu Gly Pro Ser Ser Ala

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-25
                                     -20
                                                        -15
  Leu Asn Gln Thr Leu Met Leu Leu Arg Glu Val Leu Ala Ser His Asp
                    -5
              -10
  Ser Ser Val Val Pro Leu Asp Ala Arg Gln Ala Asp Phe Val Gln Gly
                        10
                                            15
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  <211> 61
  <212> PRT
  <213> Homo sapiens
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  <221> SIGNAL
  <222> -32..-1
  <400> 1142
 Met Gly Gly Thr Ala Gly Trp Ser Ser Gln Asn Thr His Asn Ile Xaa
         -30
                            -25
                                               -20
  Val His His Leu Val Trp Leu Trp Phe Val Val Pro Gln Thr Ile Thr
     -15 .
                        -10
                                            - 5
 Met Ile Thr Pro Lys Ile Thr Glu His Arg Pro Xaa Ile Thr Asp Xaa
             5
                                   10
 Xaa Ile Met Xaa Thr Phe Glu Xaa Leu Gly Glu Leu Pro
             20
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 <210> 1143
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 <400> 1143
 Met Cys Leu Ser Val Ala Leu Tyr Leu Cys Val Cys Val Cys
         -15
                               -10
                                           -5
 Leu Ile Ala Arg Val Tyr Phe Cys Ile Tyr Val Cys Val Trp
        1
                        5
                                           10
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 <211> 29
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 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -14..-1
 <400> 1144
 Met Leu His Leu Leu Phe Gly Leu Phe Pro Val Leu Trp Met Phe Leu
                -10
                                   - 5
 Val Tyr Phe Phe Leu Ser Ser Phe Phe Phe Phe Phe
     . 5
                           10
<210> 1145
 <211> 22
 <212> PRT
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 <222> -18..-1
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 Met Tyr Val Cys Xaa Cys Val Tyr Leu Phe Cys Ala Cys Met Cys Val
            -15
                                -10
 Cys Ala Phe Phe Phe
         1
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 <213> Homo sapiens
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 <222> -36..-1
 <400> 1146
 Met Lys Xaa Asn Asn Leu Arg Arg Gln Ser Pro Ala Leu Arg His Cys
  -35
                        -30
Trp Arg Xaa Glu Thr Asp Phe Phe Leu Phe Thr Leu Ile Gly Ala Ser
                            -10
                    -15
 Leu Leu Gln Ser Ala Ser Gly Pro Cys Arg Ile Ser Xaa Xaa Leu Lys
                1
                          5
 Trp His Ser Lys Gly Thr Leu
        15
<210> 1147
<211> 54
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -20..-1
<400> 1147
Met Trp Pro Lys Xaa Gly Leu Leu Gly Leu Gly Leu Pro Leu Leu Pro
                 -15
                                      -10
Pro Asn His Pro Ser Val Ala Gln Gly Thr Leu Val Ser Ser His Ser
Gly Ser Gly Ser Glu Gly Arg Val Ala Leu Arg Ser Asp Val His Ser
                           20
Pro Lys Thr Thr Xaa Gln
  30
<210> 1148
<211> 135
<212> PRT
<213> Homo sapiens
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<222> -42..-1
<400> 1148
Met Tyr Leu Ile Arg Glu Ser His Ala Ser Gly Ser Ser Ser Val Thr
       -40
             -35
                                              -30
Ser Ser Cys Ser Leu Xaa Ser Xaa Ser Pro Asn Pro Gln Ala Met Ala
                       -20
                                          -15
Xaa Leu Phe Leu Ser Ala Pro Pro Gln Ala Glu Val Thr Phe Glu Asp
               - 5
                                      3
Val Ala Val Tyr Leu Ser Arg Glu Glu Trp Gly Arg Leu Gly Pro Ala
           10
                                                  20
```

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Gln Arg Gly Xaa Tyr Arg Asp Val Met Leu Glu Thr Tyr Xaa Asn Xaa
                              30
  Val Ser Leu Gly Val Gly Pro Ala Gly Pro Lys Xaa Gly Val Ile Ser
 Gln Leu Glu Arg Gly Asp Glu Pro Trp Val Leu Asp Val Gln Gly Thr
                     60
                                         65
  Ser Gly Lys Glu His Leu Lys Lys Ser Thr Ala Gln Leu Leu Gly Pro
                                     80
 Glu Leu Lys Tyr Lys Glu Leu
             90
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 <400> 1149
 Met Ile Pro Arg Arg Thr Ser Ala Ser Arg Ala Pro Ser Val Pro Gln
         - 35
                             -30
 Asn Ala Gly Leu Ser Pro Leu Pro Ala Leu Ser Ser Leu Cys Val Ser
                        . - 15
                                             -10
 Trp Gly Thr Ser Ser Thr Val Thr Arg Leu Arg Pro Trp Ile Ser Pro
 Thr Trp Thr Ser Arg Ala Arg
 <210> 1150
 <211> 56
 <212> PRT
 <213> Homo sapiens
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 <222> -14..-1
 <400> 1150
 Met Val Cys Ile Phe Cys Phe Leu Thr Ser Lys Ala Phe Pro Asn Pro
                ~10
                                    -5
 Arg Ser Gln Asp Phe Leu Leu Asp Phe Ser Arg His Xaa Ile Gly Leu
                            10
 Gly Phe Thr Phe Arg Ser Ala Met His Phe Glu Asn Phe Arg Leu Xaa
                        25
 Gly Leu Gly Gln Asp Ser Leu Cys
 <210> 1151
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 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
 <222> -20..-1
Met Xaa Xaa Tyr Xaa Xaa Xaa Gly Phe Cys Ser Val Thr Ser Ser Pro
                    -15
Leu Ala Ser Ala Gly Arg Thr Thr Arg
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<220>.
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<222> -23..-1
<400> 1152
Met Ser Leu Xaa Xaa Leu Cys Asp Pro Asp Leu Val Pro Cys Pro Leu
           -20
                  . -15
Leu Ile Ser Val Ala Leu Ser Val Lys Phe His Ile Xaa Gln Gln Val
     -5
                            1
Asn Leu Pro Cys Ser Ser
                    15
10
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<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -39..-1
<400> 1153
Met Met Ile Leu Ile Leu Glu His Ile Val Thr Xaa Lys Arg
               -35
                                  -30
Asn Pro Lys Pro Val Thr Val Pro Ala Phe Leu Xaa Pro Cys Leu Thr
           -20
                              -15
                                                  -10
Ser Phe Ser Cys Xaa Gly Ala Ser Phe Ser Leu Xaa Gly Xaa Arg Arg
     - 5
                           1
                                          5
Gly Trp Gln His Gly Ser Cys Cys Ser Thr Ile Pro Leu Phe Xaa Thr
                   15
                                      20
Leu Asn Ser Leu Gly Gln Gly Leu Ile Gly Pro Ala Tyr Ile Gly Ala
               30
                                   35
                                                      40
<210> 1154
<211> 19
<212> PRT
<213> Homo sapiens
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<222> -16. -1
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Met Ser Thr His Ala Ile Ser Ile Leu Leu Cys Ile Gly Ala Ser Ser
  -15
                       -10
Gln Gly Arg
1
<210> 1155
<211> 67
<212> PRT
<213> Homo sapiens
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<222> -31..-1
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<400> 1155

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Met Glu Glu Gln Glu Thr Glu Glu Val Gly Gly Arg Ser Ser Arg Lys
                          -25
                                              -20
  Asn Ala Ala Thr Val Asn Ala Ala Ser Leu Pro Pro Cys Phe Gly Val
                      -10
                                          - 5
  Lys Ser Cys Arg Cys Arg Cys Ser Cys Arg Arg Cys Leu Leu Tyr
                                  10
  Phe Ser Trp Pro Arg Gly Arg Ile Ser Pro Pro Val Gly Gln Cys Ala
         20
                              25
  Gly Arg Gly
      35
  <210> 1156
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  <221> SIGNAL
  <222> -33..-1
  <400> 1156
 Met Arg Gly Ile Gln Ala Lys Gly Ser Pro Gly Gln Ser Ser Ala Xaa
                                  -25
 Val Leu Xaa Pro Cys Cys Cys His Ala Gly Ala Ser Ser Gly Ala Thr
                             -10
 Ala Trp Glu Glu Thr Pro Arg Ser Arg Cys His Ile Ala Val Xaa Ser
                                          10
 Thr Asn Thr Ala Ser Arg Gly Arg Thr Trp Cys Arg Ala Thr Gly Pro
                                      25
 Cys Pro Ser Gly Pro Thr Arg Gly Val Ser Arg Ser Arg Gly Leu Gly
             35
                                 40
                                                      45
 Ala Gly Phe Leu Ser Pro Phe Cys Cys Leu Phe Ala Phe His Pro Arg
                             55.
                                                  60
 Leu Pro Trp Cys Ala Glu Val Pro Val Pro Ala Ala Ala His His Met
                         70
 Arg Cys Gly Gly Asp Leu Leu Ala Ala Pro Pro Pro Gly Pro Ser Trp
                     85
                                         90
 Phe Ala Arg Phe Pro Pro Leu Val Pro Glu Ser Phe Pro His His Ser
                 100
                                     105
 Val
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 <400> 1157
 Met Phe Ser Ser Arg Ser Phe Met Val Ser Gly Leu Ile Trp Val Phe
                -20
                                     -15
 Gly Leu Val Ser Val Leu Ser Xaa Phe Leu Cys Met Val Tyr Asp Gln
Gly Gln
   10
<210> 1158
<211> 31
<212> PRT
<213> Homo sapiens
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Met Leu Leu Ala Val Ser Leu Ser Leu Val Ser Asn Cys Asn Phe Val
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                  -5
                                 . 1
Leu Thr Asp Gln Leu Phe Pro Ala Pro Ala Ser Leu Ile Pro Glu
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<211> 41
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<400> 1159
Met Asn Gln Asp Phe Asn Pro Glu Ile Glu Ala Ser Pro Gln Val Lys
              -25
                  -20
Thr Gly Val Phe Leu Phe Ser Ile Ile Gly Ser Phe Gly Phe Pro Gly
       -10
                  -5
Met Cys Asn Cys Lys Asn Pro Ala Arg
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<400> 1160
Met Pro Cys Ser Trp Ser His Ile Val Ser Ser Leu Phe Ser Trp Leu
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Leu Ser Leu Thr Ser Val Pro Gly
<210> 1161
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<213> Homo sapiens
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<222> -28..-1
<400> 1161
Met Phe Phe Gly Tyr Ser Glu Asp Ile Tyr Cys Val Ser Gly Pro
    -25
                           -20
Val Leu Ser Cys Cys Cys Leu Thr Ala Gly Arg Ala Arg Leu Trp
   -10
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<210> 1162
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<213> Homo sapiens
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<222> -16..-1
 <400> 1162
Met Pro Tyr Ala Ala Leu Ile Cys Pro Trp Ser Ser Gln Val Pro Ser
  -15
                        -10
                                            -5
Ser Pro Pro Ala Ser Leu Glu Ala Ser Ser Asn Val Tyr Leu Gln Glu
                                    10
Ser Arg Ala Ala Tyr Ala Ser Val Pro Ala Gly Pro Glu Val Ala Thr
           20
Gln His Thr Ser Ser Pro Val Thr Pro Met
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<212> PRT
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<221> SIGNAL
<222> -18..-1
<400> 1163
Met Gln Leu Leu Tyr Leu Thr Tyr Ser Leu Ala Phe Leu Leu Phe Ile
           -15
                                -10
Lys Ala Gly Thr
        1
<210> 1164
<211> 24
<212> PRT
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<222> -20..-1
<400> 1164
Met Ala Pro Ser Arg Pro Arg Ala Ala Ala Val Thr Ser Ser Ala Ala
                   -15
Pro Ser Arg Ala Arg Gln Gly Ala
                1
<210> 1165
<211> 57
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
<400> 1165
Met Leu Ala Ser Ala Pro Arg Leu Asn Ser Ala Asp Arg Pro Met Lys
                           -35
                                               -30
Thr Ser Val Leu Arg Gln Arg Lys Gly Ser Val Arg Lys Gln His Leu
                       -20
                                           -15
Leu Ser Trp Ala Xaa Gln Xaa Gly Arg Xaa Gln Val Val Glu Ile Leu
                   -5
Gln Ser Glu Lys Gln Thr Xaa Xaa Asp
           10
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15

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<211> 47
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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -38..-1
<400> 1166
Met Tyr Pro Leu Gly Arg Gly Glu Gln Gly Pro Ala Ala Pro Lys Ser
         - 35
                                -30
Trp Leu Leu Pro Thr Thr Leu Ala Leu His Gly Ser Leu Asp Ala
 . -20
                            -15
                                                -10
Val Ser Gln Ala Gln Gly Arg Pro Gly His Pro Asp Ala Pro Pro
<210> 1167
<211> 21
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -16..-1
<400> 1167
Met Arg Val Phe Ile Ala Ala Leu Phe Thr Ile Ala Glu Thr Trp Asn
  -15
Gln Pro Lys Cys Pro
                5
<210> 1168
<211> 55
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
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<400> 1168
Met Ala Lys Gly Leu Arg Val Asn Leu Gly Glu Leu Val Glu Ser Met
-30
             - -25
                                       -20
Arg Leu Cys Phe Leu Ser Val His Phe Arg Leu Arg Trp Gly Asp Ser
            -10
                                   -5
Cys Pro Ser Ser Pro His Arg Glu Thr Phe Pro Ala Gly Pro Val Asn
                          10
Gly Pro Leu Tyr His Pro Arg
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<210> 1169
<211> 87
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
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<400> 1169
Met Pro Ser Pro Gln Leu Leu Val Leu Phe Gly Ser Gln Thr Gly Thr
       -15
                           -10 .
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Ala Gln Asp Val Ser Glu Arg Leu Gly Arg Glu Ala Arg Gly Arg Arg
                                         10
 Leu Gly Cys Arg Val Gln Ala Leu Asp Ser Tyr Pro Val Val Asn Leu
                 20
                                     25
 Ile Asn Glu Pro Leu Val Ile Phe Val Cys Ala Thr Xaa Gly Gln Gly
                                 40
 Asp Pro Pro Asp Asn Met Lys Asn Phe Trp Arg Phe Ile Phe Arg Lys
                             55
 Asn Leu Pro Ser Thr Ala Arg
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Met Ser Ser Ile Leu Gly Val Ser Ser Ser Trp Trp Tyr Leu Tyr Tyr
                         -35
                                            -30
Gly Tyr Cys Ile Phe Val Lys Lys Cys Ser Phe Cys Ser Phe Leu Phe
-25
                     -20
                                         -15
Leu Ala Cys Ile Phe Gln Gly Xaa Ser Xaa Xaa Xaa Asn Thr Gln Ser
                                     1
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<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<400> 1171
Met Gly Ser Val Leu Gly Leu Cys Ser Met Ala Ser Trp Ile Pro Cys
            -25
                                -20
Leu Cys Gly Ser Ala Pro Cys Leu Leu Cys Arg Cys Cys Pro Ser Gly
  -10
                            -5
Asn Asn Ser Thr Val Thr Arg Leu Ile Tyr Ala Leu Phe Leu Leu Val
                                        15
Gly Val Trp
<210> 1172
<211> 109
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
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<400> 1172
Met Ser Xaa Xaa Xaa Arg Leu Xaa Arg Gln Leu Leu Ser Gln Xaa Arg
                        -40
Xaa Met Thr Cys Glu Asn Glu Ala Gly Ala Gln Cys Gln Lys Ser Ser
                    -25
                                        -20
Phe Ile Gly Ser Cys Ser Val Met Ser Ser Gly Ala Leu Cys Val Pro
```

Leu Tyr Tyr Leu Ala Lys Gly Asn Met Cys Ser Ile Cys Gly Met Leu

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10
 Lys Glu Met Asn Gly Leu Trp Ser Glu Cys Asp Ser Leu Lys Asn Thr
                        25
                                           30
 Phe Ile Val Trp Xaa Cys Ile Phe Ser Cys Leu Gly Met Gln Leu Xaa
                    40
                                        45
 Ser Ser Xaa Val Ser Asn Val Arg Leu Leu Ser His
                55
 <210> 1173
 <211> 64
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
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<400> 1173
Met Pro His Pro Leu Ala Thr Ser Ala Phe Leu Arg Ser Ala Phe Pro
                       -20
                                      -15
Phe Val Cys Leu Thr Phe Cys Val Gly Gly Pro Gly Ile Ser Gly
                    -5
Val Tyr Arg Leu Leu Met Ala Asn Ala Thr Arg Arg Glu Ser Glu Val
           10
                               15
Ser Leu Arg Gly Leu Gly Arg Asp Gly Glu Gly Ala Arg Ala Thr Pro
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                                               35
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<211> 27
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 1174
Met Thr Val Gly Leu His Ile Leu Arg Asp Ser Leu Met Val Phe Leu
           -20
                             -15
                                                   -10
Asn Leu Phe Phe Leu Asn Cys Asp Pro His Arg
       -5
                           1
<210> 1175
<211> 35
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -21..-1
<400> 1175
Met Val Arg Trp Gly His Pro Pro Met Phe Cys Val Ser Leu Leu Leu
                       -15
                                         -10
His His Ala Tyr Pro Leu Pro Ser Thr Met Ile Val Ser Phe Pro Arg
Pro Pro Leu
<210> 1176
<211> 93
<212> PRT
<213> Homo sapiens
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<220>
<221> SIGNAL
 <222> -26..-1
 <400> 1176
Met Ala Gly Ala Ala Arg Trp Val Gly Gln Xaa Ser Ser Ala Met Val
                        -20
                                            -15
Cys Phe Gly Cys Pro Gly Gly Ala Ser Ser Arg Cys Arg Ser Pro Arg
                    -5
                                        1
Gly Arg Gln Ala Ser Arg Val Pro Arg Leu Glu Asn Gly Ala Gln Arg
            10
                                15
Val Val Arg Thr Met Val His Leu Val Leu Gln Pro Lys Arg Val Thr
 25
                            30
Leu Val His Pro Pro Arg Gly Leu Glu Pro Val Cys Thr Pro Ile Ala
                       45
Xaa Met Xaa Pro Lys Ser His Gly Leu Arg Ser Ser Leu
                    60
<210> 1177
<211> 47
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -34..-1
<400> 1177
Met Gly Val Val Ser Gly Gly Val Gly Asp Leu Thr Thr Lys Thr Gln
               -30
                                   -25
                                                       -20
Glu Asn Gly Leu Leu Pro Xaa Leu Leu Ser Xaa Leu His Gly Leu Leu
     -15
                               -10
                                                   -5
Tyr Gly Ser Pro Asp Ala Glu Leu Thr Gly Pro Asp Pro Trp Asp
      1
                       5
<210> 1178
<211> 17
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -15..-1
<400> 1178
Met Gly Phe Leu Ser Xaa Thr Cys Val Leu Ser Cys Xaa Arg Ser Leu
-15
                   -10
Ser
<210> 1179
<211> 48
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -39..-1
<400> 1179
Met Glu Tyr Gly Ser Ala Lys Leu Ser Ser Gly Arg Val Phe Tyr Leu
               -35
                          -30
Pro Arg Asp Phe Gly Ile Glu Arg Arg Val Leu Val Cys Phe Phe Asn
           -20
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Ser Val Ser Phe Leu Phe Gly Val Ser Xaa Lys Lys Ser Xaa Gln Trp
                             1
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 <211> 17
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
 <222> -13..-1
<400> 1180
Met Leu Ser Gly Leu Val Leu Asn Ser Trp Ala Leu Ala Tyr Gln Leu
Ala
<210> 1181
<211> 23
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 1181
Met Arg Leu Val Phe Phe Xaa Gly Xaa Ser Ile Ile Leu Val Leu Gly
         -10
 -15
Ser Thr Phe Xaa Ala Tyr Leu
<210> 1182
<211> 35
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 1182
Met Leu Ser Ser Asp Phe Phe Leu Leu Phe Val Ser Leu Ser Leu Ser
                        -10
                                            ~5
Pro Phe Pro Phe Leu Phe Pro Pro Leu Phe Ser Cys Phe Leu Leu
1 .
                                    10
Pro Thr Arg
<210> 1183
<211> 58
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
<400> 1183
Met Phe Ile Ala Ala Leu Phe Thr Val Ala Lys Ile Trp Asn Gln Pro
               -10
                                   - 5
Lys Cys Pro Ser Thr Asp Glu Trp Ile Asn Lys Met Trp Tyr Ile Tyr
                           10
                                               15
Thr Met Glu Tyr Tyr Pro Asp Ile Lys Lys Asn Gly Ile Leu Thr Phe
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Lys Ala Thr Arg Met Asn Arg Lys Thr Leu
                  40
 <210> 1184
 <211> 31
 <212> PRT
 <213> Homo sapiens
<220>
<221> SIGNAL
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<400> 1184
Met Cys Val Cys Gly Cys Leu Cys Val Trp Met Cys Val Cys Gly Xaa
-15 -10
                           -5
Val Cys Ile Tyr Ile Xaa Val Tyr Val Cys Thr Cys Val Arg Gly
                           10
<210> 1185
<211> 61
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 1185
Met Gly Val Arg Thr Val Cys His Phe Ile Gln Val Phe Leu Ser Leu
   -25
                     -20
Phe Val Phe Phe Trp Leu Val Gly Phe Ser Phe Phe Phe Leu Xaa
-10 -5
                                    1
Phe Ser Thr Lys Gln Val Arg Val Glu Gln His Cys Asp Phe Lys Ser
   10 15
Thr Pro Xaa Val Glu Ser Ser Ser Thr Val Gly His Ala
                         30
<210> 1186
<211> 63
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -27..-1
<400> 1186
Met Tyr His Ile Leu Phe Ile His Ser Phe Ile Asp Arg Tyr Leu Ser
    -25
                         -20
                                 -15
Cys Phe Tyr Leu Leu Ala Ile Val Ser Asn Ala Val Met Asn Met Gly
                     - 5
                                        1
Val Gln Met Ser Val Leu Ser Pro Cys Phe Ala Phe Val His Ser Ile
              10
                                15
Lys Asn Val Lys Val Leu Cys Phe Leu Leu Phe Phe Leu Phe Gly
                            30
<210> 1187
<211> 37
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
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Met Gln Phe Thr Val Leu Met Cys Pro Val Gln Trp Leu Leu Val Tyr
                            -15
Ser Pro Ser Cys Ala Ala Thr Ile Thr Val Asn Phe Lys Thr Phe Ser
                         1
                                         5
Ser Pro Gln Thr Gly
<210> 1188
<211> 40
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 1188
Met Arg Arg Ala Trp Thr Gln Glu Arg Glu Pro Arg Pro Cys Glu Pro
                     . - 30 .
Ala Glu Arg Ala Asp Pro Ala Pro Val Ser Cys Leu Ser Ala Gly Leu
                        -15
  -20
Arg Val Cys Cys Ser Gln Arg Ser
-5
<210> 1189
<211> 37
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 1189
Met Leu His Leu Ile Cys Ile Ser Leu Ile Val Asn Asp Phe Phe Ile
-25
                   -20
                                        -15
Cys Leu Leu Ala Ile Cys Val Ser Ser Phe Glu Asn Cys Leu Phe Met
                - 5
                                                    5
Ser Leu Ala His Ser
       10
<210> 1190
<211> 96
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -63..-1
<400> 1190
Met Arg Ser Glu Arg Pro Met Val Trp Cys Cys Leu Phe Val Arg Ser
           -60
                                -55
                                                    -50
Gln Arg Lys Arg Lys Gln Ser Thr Gln Asp Glu Asp Ala Val Ser Leu
       -45
                            -40
                                                -35
Cys Ser Leu Asp Ile Ser Glu Pro Ser Asn Lys Arg Val Lys Pro Leu
                        -25
                                            -20
Ser Arg Val Thr Ser Leu Ala Asn Leu Ile Pro Pro Val Lys Ala Xaa
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<220>

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Pro Leu Lys Arg Phe Ser Gln Thr Leu Gln Arg Ser Ile Ser Phe Arg
                            10
 Ser Glu Ser Arg Pro Asp Ile Leu Ala Pro Arg Pro Trp Ser Arg Asn
                            25
 <210> 1191
 <211> 48
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
 <222> -20..-1
 <400> 1191
Met Val Phe Trp Thr Lys Phe Cys Ile Leu Ile Ser Thr Ala Phe Pro
                  -15
Ser Leu Leu Thr Gln Ile Ile Phe Pro Lys Ser Ile Thr Phe Ala Phe
             1 .
                                                    10
Gln Phe Phe Trp Asn Arg Glu Lys Gln Lys Thr Lys Thr Pro Thr Gly
                            20
                                               25
<210> 1192
<211> 65
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 1192
Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu Ala Ala Cys Gly Ile
                     -30
                                               -25
Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile Met Leu Gly Ile Phe
   -20
                       -15
                                           -10
Phe Asn Val His Ser Ala Val Leu Ile Glu Asp Val Pro Phe Thr Glu
- 5
                   1
Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr Asn Leu Tyr Glu His
          15
                               20
Gly
<210> 1193
<211> 28
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 1193
Met Ser Val Ser Ala Leu Leu Glu Xaa Leu Gln Xaa Ala Ile Pro
                       -10
Arg Xaa Thr Ser Gly Xaa Gln Asp Leu Pro Asn Trp
<210> 1194
<211> 50
<212> PRT
<213> Homo sapiens
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<222> -41..-1

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<221> SIGNAL
 <222> -39..-1
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Met Gln Ala Cys Tyr Met Gly Met Trp Tyr Thr Ala Glu Ala Trp Gly
               -35
                                 -30
                                                       -25
 Thr Ile Glu Ser Leu Thr Gln Val Val Ser Val Ile Ala Ile Val Ser
           -20
                                -15
                                                 -10
 Phe Thr Thr Leu Cys Ser Ser Leu Tyr Ser Pro Gln Val Val Pro Ser
                                           5
Val Gly
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<210> 1195
<211> 67
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -62..-1
<400> 1195
Met Met Leu Arg Gly Gly Gly Thr Phe Lys Xaa Cys Leu Ser His Glu
  -60
                           -55
                                               -50
Gly Ser Ser Phe Thr Lys Gly Leu Ala Gln Glu Cys Val Ser Xaa Ser
 -45
                       -40
                                           -35
Cys Gly Thr Arg Leu Ile Thr Ala Val Ala Ser Xaa Tyr Lys Ala Arg
               -25
                                    -20
Leu Pro Leu Ala Ala Cys Pro Leu Leu Pro Ile Phe Ser His Ala
              . -10
                                  - 5
Arg Ser Ser
       5
<210> 1196
<211> 68
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -40..-1
<400> 1196
Met Ala Lys Asn Pro Pro Glu Asn Cys Glu Asp Cys His Ile Leu Asn
                -35
                                       -30
Ala Glu Ala Phe Lys Ser Lys Lys Ile Cys Lys Ser Leu Lys Ile Cys
               -20
                                   -15
                                                      -10
Gly Leu Val Phe Gly Ile Leu Ala Leu Thr Leu Ile Val Leu Phe Trp
           ~5
Gly Ser Lys His Phe Trp Pro Glu Val Pro Lys Lys Ala Tyr Asp Met
                      15
  10
Glu His Thr Thr
25
<210> 1197
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<212> PRT
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<220>
<221> SIGNAL
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<4.00> 1197
 Met Ser Pro Ala Pro Asp Ala Ala Pro Ala Pro Ala Ser Ile Ser Leu
                        -35
                                            -30 ·
 Phe Asp Leu Ser Ala Asp Ala Pro Val Phe Gln Gly Leu Ser Leu Val
              -20
                                     -15
 Ser His Ala Pro Gly Glu Ala Leu Ala Arg Ala Pro Arg Thr Ser Cys
                 - 5
                                    1
 Ser Gly Ser Gly Glu Arg Glu Ser Pro Glu Arg Lys Leu Leu Gln Gly
                            15
 Pro Met Asp Ile Ser Glu Lys Leu Phe Cys Ser Thr Cys Asp Gln Thr
                         30
 Phe Gln
 40
 <210> 1198
·<211> 56
<212> PRT
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<221> SIGNAL
<222> -35..-1
<400> 1198
Met Leu Leu His Tyr Leu Lys Leu Lys Gly Asp Gln Trp Lys Leu Ser
                    -30
                                        -25
Ser Val Ser Thr Leu Ile Leu Phe Ile Phe Ile Gly Ser Leu Gln Pro
             -15
                                 -10
                                                        - 5
Val Pro Thr Arg Phe Lys Arg Phe Ser Cys Leu Xaa His Leu Ser Ser
            1
Arg Asp His Arg Gln Ala Leu Arg
<210> 1199
<211> 184
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -153..-1
<400> 1199
Met Ala Glu Gly Asp Asn Arg Ser Thr Asn Leu Leu Ala Ala Glu Thr
           -150
                               -145
                                                   -140
Ala Ser Leu Glu Glu Gln Leu Gln Gly Trp Gly Glu Val Met Leu Met
                           -130
                                               -125
Ala Asp Lys Val Leu Arg Trp Glu Arg Ala Trp Phe Pro Pro Ala Ile
                       -115
                                           -110
Met Gly Val Val Ser Leu Val Phe Leu Ile Ile Tyr Tyr Leu Asp Pro
                   -100
                                       -95
Ser Val Leu Ser Gly Val Ser Cys Phe Val Met Phe Leu Cys Leu Ala
               -85
                                   -80
Asp Tyr Leu Val Pro Ile Leu Ala Pro Arg Ile Phe Gly Ser Asn Lys
           -70
                               -65
Trp Thr Thr Glu Gln Gln Arg Phe His Glu Ile Cys Ser Asn Leu
       -55
                           -50
Val Lys Thr Arg Arg Arg Ala Val Gly Trp Trp Lys Arg Leu Phe Thr
                       -35
                                           -30
Leu Lys Glu Glu Lys Pro Lys Met Tyr Phe Met Thr Met Ile Val Ser
                   -20
                                      -15
Leu Ala Ala Val Ala Trp Val Gly Gln Gln Val His Asn Leu Leu
```

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-5
  Thr Tyr Leu Ile Val Thr Ser Leu Leu Leu Leu Pro Gly Leu Asn Gln
                             15
                                                  20
  His Gly Ile Ile Leu Lys Tyr Ile
  <210> 1200
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  <222> -26..-1
  <400> 1200
  Met Ala Ala Leu Lys Ala Leu Val Ser Gly Cys Gly Arg Leu Leu Arg
                         -20
                                             -15
  Gly Leu Leu Ala Gly Pro Ala Ala Thr Ser Trp Ser Arg Leu Pro Ala
                   -5
  Arg Gly Phe Arg Glu Val Val Glu Thr Gln Glu Gly Lys Thr Thr Ile
                                 15
  Ile Glu Gly Arg Ile Thr Ala Thr Pro Lys Glu Ser Pro Asn Pro Pro
  Asn Pro Ser Gly Gln Cys Pro Ile Cys Arg Trp Asn Leu Lys His Lys
                         45
  Tyr Asn Tyr Asp Asp Val Leu Leu Ser Gln Phe Ile Arg Pro His
              . 60
  Gly Gly Met Leu Pro
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  <211> 44
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  <213> Homo sapiens
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  <221> SIGNAL
  <222> -23..-1
  <400> 1201
 Met Gly Ser Leu Leu Phe Ile Arg Gln Thr Leu Val Gly Phe Lys Gln
             -20
                                -15
                                                     -10
 Val Val Ala Trp Thr Phe Ala Ser Asp Ser His Cys Xaa Xaa Val Xaa
   -5
                             1
 Met Val Xaa Xaa Ser Gln Leu Xaa Asn Pro Pro Leu
 <210> 1202
 <211> 48
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -24..-1
 <400> 1202
 Met Leu Ala Arg Ala Ala Glu Xaa Thr Gly Ala Leu Leu Leu Arg Gly
                -20
                                    -15
                                                         -10
 Ser Leu Leu Ala Ser Xaa Arg Ala Xaa Xaa Pro Pro Leu Gly Leu
· Xaa Arg Asn Thr Xaa Gly Thr Val Arg Ala Ala Ala Gly Gly Leu Gly
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<210> 1203

<211> 28

<212> PRT

<213 > Homo sapiens

<220>

<221> SIGNAL

<222> -17..-1

<400> 1203

Met Asn Ala Ser Leu Leu Ser Phe Cys Leu Cys Ser Asp Phe Ile Ser -15 -10

Gln Asp Ala Leu Leu Thr Val Ile Phe Pro Pro . 5 1 10

<210> 1204

<211> 79

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -60..-1

<400> 1204

Met Leu Asn Met Glu Pro Tyr Thr Val Ser Gly Met Ala Arg Gln Asp -50 -55

Ser Ser Ser Glu Val Gly Glu Asn Gly Arg Ser Val Asp Gln Gly Gly -40 -35

Gly Gly Ser Pro Arg Lys Lys Val Ala Leu Thr Glu Asn Tyr Glu Leu -25 -20 -15

Val Gly Val Ile Val His Ser Gly Gln Ala His Ala Gly His Tyr Tyr -10 - 5

Ser Phe Ile Lys Asp Arg Arg Gly Cys Gly Lys Gly Lys Trp Leu 10

<210> 1205

<211> 23

<212> PRT

<213> Homo sapiens

<220>

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<222> -20..-1

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Met Xaa Xaa Ala His Phe Ser Leu His Leu Xaa Ser Ser Arg Xaa Pro -15 -5

Pro Ile Leu Ala Ser Pro Val

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  Ala Ile Tyr Ile Ser Pro Ser Val Asn Cys Leu Phe Ile Ser Phe Pro
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 Leu Leu Ser Ala Arg Leu Leu Ser Gln Glu Lys Arg Ala Ala Glu Thr
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                                 -5
 His Phe Gly Phe Glu Thr Val Ser Glu Glu Glu Lys Arg Gly Asp Leu '
                        10
 Thr Ser Val Val Ser Leu Glu Tyr Pro Glu Val Gln Leu Gln Gly Gln
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 Arg Val Tyr Ala Phe Leu Ser Pro Ile Cys Thr Tyr Gly Ser Glu Gly
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 Cys Ser Leu Lys
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 Met Glu Asn Leu Pro Phe Pro Leu Lys Leu Leu Ser Ala Ser Ser Leu
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                                        -25
 Asn Thr Pro Ser Ser Thr Pro Trp Val Leu Asp Ile Phe Leu Thr Leu
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                                    -10
                                                         - 5
 Val Phe Ala Leu Gly Phe Phe Phe Leu Leu Pro Tyr Phe Ser Tyr
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 Leu Arg Cys Asp Asn Pro Pro
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 Val Arg Cys Ile
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                                    -35
Arg Thr Ala Ala Glu Gln Val Gly Cys Lys Gln Arg Ser Phe His Xaa
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                                -20
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Pro Cys Pro Leu Leu Phe Pro Gly Ala Cys Phe Pro Cys Pro
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Met Asn Leu Ile Cys Val Ser Leu Met Ala Ser Asp Gly Ala Ser Ser
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Pro Val Leu Gly Gly Ser Ser His Ser Ser Ser Xaa Xaa
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Met Gly Ser Val Thr Gly Ala Val Leu Lys Thr Leu Leu Leu Leu Ser
       -45
             -40
Thr Gln Asn Trp Asn Arg Val Glu Ala Gly Asn Ser Tyr Asp Cys Asp
                       -25
                                         -20
Asp Pro Leu Val Ser Ala Leu Pro Gln Ala Ser Phe Ser Ser Ser Ser
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Glu Leu Ser Ser Ser His Ser Pro Gly Phe Ala
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Met Met Ser Glu Xaa Ser Gln Asp Leu Val Val Lys Cys Ala Pro Pro
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Xaa Pro Phe Phe Leu Leu Phe Leu Phe Ser Ser Cys Asp Val Pro Val -15 -10 -5 Pro Leu His Leu Leu Gln Trp Leu Gln Ser Phe Leu Arg Pro Arg 5 10 <210> 1214 <211> 59 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -27..-1 <400> 1214 Met Phe Arg Cys Val Arg Phe Leu Pro Ser Gly Gly Phe Val Val Leu -20 Leu Thr Ser Gly Val Lys Pro Gln Thr Phe Ala Val Ser Val Thr Ala - 5 1 Leu Lys Gly Gly Met Pro Gly Val Val His Ser Ser Gly Gly Phe Val 10 15 . Val Leu Leu Thr Ser Gly Ala Xaa Cys Arg Pro 25 30 <210> 1215 <211> 52 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1 <400> 1215 Met Arg Val Gly Arg Arg Glu Gly His Pro Leu Phe Pro Asn Val Pro -25 -20 Arg Cys Leu Phe Leu Asn Ala Arg Leu Ala Gly Thr Leu Cys Gln Leu -10 -5 Lys Leu Leu Gln Phe Gly Arg Leu Gly Asn Thr Glu Ser His Leu His 10 15 Gly Leu Ala Gly 20 <210> 1216 <211> 33 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -31..-1 <400> 1216 Met Tyr Phe Asp Ile Gln Ile Val Ser Asp Val Val Ser Gly Ile Pro -30 -25 -20 Phe Lys Leu Cys Pro Leu Thr Cys Pro His His Ser Leu Ser Thr -15 -10 -5 Val <210> 1217 <211> 47 <212> PRT <213> Homo sapiens

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                        -25
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 Phe Ser Phe Ser Pro Phe Leu Pro Ser Leu Pro Leu Leu Glu Ala Glu
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                                        -5
Arg Met Arg Val Ser Asp Gln Leu Gln Tyr Thr Thr Gly Xaa Gly
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Met Glu Leu Glu Ala Met Ser Arg Tyr Thr Ser Pro Val Asn Pro Ala
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                                            - 25
Val Phe Pro His Leu Thr Val Val Leu Leu Ala Ile Gly Met Phe Phe
                    -15
                                        -10
Thr Ala Trp Phe Phe Val Tyr Glu Val Thr Ser Thr Lys Tyr Thr Arg
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                               5
Asp Ile Tyr Lys Glu Leu Leu Ile Ser Leu Val Ala Arg
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Met Lys Gly Ala Leu Lys Leu Ile Ser Thr Asn Phe Ser Leu Cys Gln
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                                     -5
Ser Val Gln Cys Pro Ser Glu Glu Thr Ile Thr Asp Leu Val Ser Val
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Pro Cys Gln Xaa Gly Leu
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Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser
               -65
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Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln
           -50
                               -45
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557
Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Ile Lys Val Ile
                            -30
Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile
                        -15
                                            -10
Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser
Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Gly
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Met Val Asp Glu Cys Leu Thr Glu Pro Val Trp Gly Ser Lys Arg Gln
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Gly Cys Ser Ser Gln Ala Glu Ala Ser Cys Asp Ile Val Ser Ala Ala
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Cys Lys Cys Gly Ser Ser Gln Ala Ala Ile Asp Cys Glu Thr Ser Ser
Cys Ser Glu Asp Phe Pro Val
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Met Ala Trp Trp Phe Ser Gly Thr Phe Pro Leu Thr His Pro Cys Ser
               -10
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Gly Tyr Gly Ser Leu Met Ala Pro Ser Ser Pro Thr Pro Ser Gly
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Met Val Ala Lys Asp Tyr Pro Phe Tyr Leu Thr Val Lys Arg Ala Asn
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       -55
Cys Ser Leu Glu Leu Pro Pro Ala Ser Gly Pro Ala Lys Asp Ala Glu
                                            -30
                        -35
Glu Pro Ser Asn Lys Arg Val Lys Pro Leu Ser Arg Val Thr Ser Leu
                                        -15
                   -20
-25
Ala Asn Leu Ile Pro Pro Val Lys Ala Thr Pro Leu Lys Arg Phe Ser
                -5
Gln Thr Leu Gln Arg Ser Ile Ser Phe Arg Ser Glu Ser Ala
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Met Ser Pro Ala Phe Arg Ala Met Asp Val Glu Pro Arg Ala Lys Gly
                               -20
         -25
Val Leu Leu Glu Pro Phe Val His Gln Val Gly Gly His Ser Cys Val
                           - 5
       -10
Leu Arg Phe Asn Glu Thr Thr Leu Cys Lys Pro Leu Val Pro Arg Glu
                                       15
                 . 10
His Gln Phe Tyr Glu Thr Leu Pro Ala Glu Met Arg Lys Phe Thr Pro
                                    30
               25
Gln Tyr Lys Gly Gln Ser Gln Arg Pro Leu Val Ser Trp Pro Ser Leu
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Pro His Phe Phe Pro Trp Ser Phe Pro Leu Trp Pro Gln Gly
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Met Leu Gly Gly Ala Val Ile Ala Gly Arg Pro Leu Gly Arg Trp Glu
                                                      - 20
               -30
                                    -25
Ser Thr Ala Gln Xaa Ile Leu Ala Phe Leu Gln Ser Pro Arg Ala Ile
                                                    - 5
                                -10
           -15
Leu Pro Gly Asn Phe Phe Glu Lys Asn Ala Gln Ile Gln Gly Gly Pro
Trp Gly Gly Ser Gly Lys Thr Cys Ala Pro Gly Arg Xaa Asp Pro
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Gly Trp Glu Cys Gly Ala Gly Gly Gly Xaa Gly Glu Ala Ala Gly Ser
                                    40
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Arg Xaa Arg Xaa Ser
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<221> SIGNAL
<222> -16..-1
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Met Ser Met Ala Cys Phe Phe His Leu Phe Val Ser Ser Leu Ile Ser
                 -10
Phe Glu Gln Cys Phe Xaa Met Leu Arg Lys Leu Leu Lys Ile Ile
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Met Gly Ser Arg Gly Asp Pro Leu Ile Cys Gly Leu Gln Arg Ser Val
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                         -35
Gly Glu Val Trp Phe Pro Gly Trp Gly His Thr Ile Thr His Cys Phe
                                 -20
               -25
Pro Trp Leu Glu Val Gly Leu Phe Phe Trp Leu His Ala Ala Pro Gly
           -10
Arg Ala Ile Ala Leu Pro His Phe Ser Ser Phe Ser Val Gly Gln Xaa
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Val His Leu Val Ser Pro Leu Xaa Xaa Leu Asp Ile Ser Val Glu
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Met His Leu Leu Gln Glu Glu Leu Leu Leu Leu Pro Arg Gly Leu
                                 -10
              -15
Cys Gln Val Cys Pro Arg Leu Cys Leu Gln Arg Xaa Val Gly Glu Leu
         1 5
Gln Xaa Xaa Xaa Pro Asp Val Gly Thr Ala Leu Leu Pro Asp Val Asn
Arg Thr Ser Cys Thr Thr Trp
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Met Cys Leu Ser Cys Ile Gln Gly Ser Phe Phe Val Glu Ile Leu Gln
           -25
                  · -20
Leu Val Thr Arg Leu Leu Leu Ser Pro Ser Gln Ser Thr Gln Thr His
       -10
Thr His Thr His Thr His Thr
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                  -25
    -30
Lys Asp Thr Ala Ile Leu Leu Leu Val Xaa Val Ser Asp Lys Asn Glu
                        -10
Gln Gln Leu Gly Arg Gly Val
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Met Arg Leu Ser Ser Cys Gly Leu Pro Val Lys Thr Leu Pro Phe '
                                                        -15
                                   ~20
Ile Cys Cys Asn Leu Tyr Phe Leu Leu Phe Cys Arg Ser Ser Phe Leu
                                - 5
            -10
Tyr Phe Gly Tyr Asp Pro Ile Asn Thr Tyr Met Tyr Tyr Asn Val Phe
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Ser His Ser
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Met Leu Leu Thr Arg Pro Ala Val Ser Ala Gly Gly Ala Xaa Arg Phe
                      -60
            -65
 Ser Pro Gly Ser Arg Gly Arg Gly Ser Asp Leu Glu Arg Gly Leu Cys
                                                -40
                            -45
        -50
 Pro Ala His Pro Gly Ala Pro Pro Leu Pro Arg Pro Pro Asp Arg Leu
                                            -25
                        -30
    -35
 Pro His Ser Phe Ser Pro Thr Gly Cys Leu Leu Xaa Pro Leu Leu Val
                                        -10
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 Ser Cys Leu Gly Ser Leu Leu Pro Val Thr Gln Thr Leu Gly Ser Phe
 Ser Ala Gly Pro Cys Phe Arg Thr Leu
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 Met His Ser Leu Cys Pro Leu Ser Gln Phe Leu Pro Ile Leu Xaa Ser
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-15
-25
                    -20
Leu Ser Ser Ser Val Pro Ser Arg Ala Gly Ser Ala Phe Pro Ser Ala
                - 5
Leu Gly Pro Leu Tyr Gln Pro Leu Leu Gly Pro Pro Ala Trp
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Met Arg Thr Gln Val Tyr Glu Gly Leu Cys Lys Asn Tyr Phe Ser Leu
            -40
                                    -35
Ala Val Leu Gln Arg Asp Arg Ile Lys Leu Leu Phe Phe Asp Ile Leu
            -25
                                -20
                                                    -15
Val Phe Leu Ser Val Xaa Leu Leu Phe Leu Leu Phe Leu Val Asp Ile
                            -5
Met Ala Asn Xaa Thr Thr Ser Leu Gly Arg Pro
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Met Gly Gln Phe Thr Ala Ala Met Val Gly Arg Ile Ser Cys Leu Gly
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Val Trp Lys Leu Pro Arg Val Glu Ser Cys Ser Gln Pro Ala Arg Pro
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                                    -20
                                                        -15
Leu Leu Ser Leu Ala Gln Thr Thr Thr Lys Thr Thr Ala Thr Thr Thr
            -10
                                -5
Thr Thr Thr Lys His Ala Thr Cys Ala Leu Ala Tyr Thr Asn Thr Pro
                        10
                                            15
Thr Glu Pro Xaa Gln Ala Asp Lys Ala Ser Arg Arg Ala Ser Gly Xaa
                   25 .
                                        30
Leu Xaa Xaa Ala Ala Arg His Ile Pro Trp His Gly Ala Thr Ala Ala
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                                   45
Gln Leu Pro Ala Pro Pro Pro Ser Val Ile Ser Ala Leu
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Met Leu Ile Phe Ile Ile Ala Ile Leu Phe Pro Asn Ser Gly Ser Cys
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                               -10
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Phe Ala Phe Ser Cys His Val Ser Phe Phe Phe

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Met Val Arg Cys Ala Cys Phe Pro Phe Pro Phe Ala Phe Cys His
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Asp Cys Lys Phe Leu Gly Ala Ser Gln Ser Cys Phe Leu Leu Ser Arg
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                              10
Gln Asn Cys Val Ser Thr Gly Xaa Pro Ser Ser Lys Ser Asp Ile Asn
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                          25
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Ser Arg Ser Gly Ser Cys Ser Leu Ala Arg
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Met Val Ser Leu Arg Val Gly Ala Ser Pro Phe Arg Phe Pro Leu Ala
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                                               -15
      -25
Pro Leu Xaa Leu Val Phe Ile Ser Leu Leu Pro Ala Pro Phe Phe Pro
   -10 ·
Thr Leu Ser Phe Pro Cys Cys Cys Val Ser Trp Leu Phe Ser Leu Ser
               10
                                 . 15
Val Xaa Val Ser Leu Arg Leu Ser Leu Xaa Val Ser Cys Leu Ser Leu
                                                   35
                               30
Trp Cys Leu Leu Val Leu Phe Leu Ser Pro Thr Leu Tyr Val Ser Asp
                           45
Ser Phe Cys Ser Phe Cys Val Leu Pro Ile Ala Leu Cys Pro Xaa Ala
                    60
Arg Ser
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Met Ala His Pro Cys Leu Ala Pro Ala Glu Pro Ser Thr Leu Ser Gln
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               -50
Thr Xaa His Pro Ile Gln Arg Thr Leu Thr Thr Phe Pro Gln Ala Trp
                                                    -25
                               -30
           -35
Val Leu Thr Ser Ser Phe Ser Ile Gln Pro Gly Leu Ala Phe Leu Ala
```

-15 Ile Leu Thr Val Leu Ala Lys Pro Gly Ser Ser Xaa Trp Ser Pro Gly

-10

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. 5
Gln Phe Thr Pro His Ser Leu Leu
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Met His Phe Pro Ile Gln Ala Thr Phe Xaa Tyr Ser Pro Thr Asp Ser
                       -25
                                            -20
Leu Cys His Leu Tyr Xaa Ser Leu Phe Ser Ser Phe Leu Cys Ser Thr
                   -10
Pro Ala Arg
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Met Ala Leu His Ile Leu Glu Cys Glu Arg Asn Val Cys Phe Val Ala
                        -30
                                            -25
Val Arg Gln Pro Ala His Glu Ser Cys Phe Val Pro Ser Leu Val Thr
                    -15
                                        -10
Gly Ala Leu Gln Gln Ser Gln Thr Gln His Pro Pro Trp Val Cys Pro
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Gln Val Gln Gly Ser Tyr Pro Ser Trp Lys Asn Arg Gly
                            20
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Met Ser Cys Thr His Ser Ser Ser Asn Leu Gly Lys Phe Ser Val His
       -30
                            -25
Arg Glu Tyr Arg Val Leu Xaa Leu Cys Asn Ser Arg Val Ser Phe Thr
  -15
                       -10
                                            -5
Arg Xaa His Val Lys Arg Pro Pro Xaa Arg Leu Cys Val Ser Ser Lys
Gly Cys Leu Phe His Leu Gly Ala Gly Arg
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Leu Phe Gln Lys Gln Xaa Gly Leu Leu Lys Asn Tyr Xaa Ser Pro Gln
Arg Gln Val Leu Phe Cys Asn Arg
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Met Ser Tyr Phe Arg Cys Ile Phe Leu Ala Val Leu Ser Lys Ile Ser
                                -10
Trp Ala Val Asn Met Cys Ser Leu Ile Ser Gly Ser Ser
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Met Leu Cys Ile Met Phe Gly Ile Glu Thr Asn Glu Ile Thr Lys Met
                -30
                                    -25
                                                         -20
Thr Met Ser Phe Leu Leu Phe Leu Ser Ile Ser Leu Ile Thr Leu Tyr
            -15
                                -10
Tyr Ser Ser Glu Ala Cys Gly
        1
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Met Cys Gln Ala Arg Ile Ala Leu Asp Arg Cys Asn Leu Arg Thr Ala
               -35
                                    -30
Phe Ile Leu Phe Xaa Leu Ile Leu Ser His Tyr Val Phe Xaa Leu Leu
           -20
                                -15
                                                    -10
Ala Pro Phe Leu Thr Arg Ser Ser Pro Ser Trp Asn Ser Tyr Gly Thr
                           7
Leu Ala Pro Glu Thr Thr Asn Ser Ser Leu Lys Phe Ser Asn Ser Asn
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20

Asn Gly Ile Ser Asp Leu Ala Xaa Leu Tyr Phe Ser His Val Xaa Lys

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565
                  30
                                                          40
 Ile Gly Ser Ala Ser Thr Met Gly Tyr Gly
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                                     -15
 Ala Ile Leu Glu Xaa Cys Gly Ala Ile Pro Lys Ile His Ser Ala Arg
 Val Ser Val Gly Glu Gly Thr Val Ala Ala Gly Tyr Gln Asp Phe Ile
                         15
                                             20
 Ile Cys Val Glu Met Phe Phe Ala Ala Leu Ala Leu Arg His Ala Phe
                     30
                                         35
 Thr Tyr Lys Val Tyr Ala Asp Lys Arg Leu Asp Ala Gln Val Pro Thr
                                     50
 Tyr Gly Pro Tyr Gly Arg Cys Ala Pro Met Lys Ser Ile Ser Ser Ser
 Leu Lys Glu
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 Met Asp Met Arg Trp His Cys Glu Asn Ser Gln Thr Thr Asp Asp Ile
                         -80
                                             -75
 Leu Val Ala Ser Ala Glu Cys Pro Ser Asp Asp Glu Asp Ile Asp Pro
                    -65
                                         -60
 Cys Glu Pro Ser Ser Gly Gly Leu Ala Asn Pro Thr Arg Ala Gly Gly
                -50
                                     -45
 Arg Glu Pro Tyr Pro Gly Ser Ala Glu Val Ile Arg Glu Ser Ser Ser
                                 -30
                                                     -25
 Thr Thr Gly Met Val Val Gly Ile Val Ala Ala Ala Ala Leu Cys Ile
 Leu Ile Leu Leu Xaa Ala Met Tyr
    -5
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 Met Ala Trp Thr Pro Leu Trp Pro Thr Leu Leu Thr Leu Cys Ile Gly
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 Ser Val Val Ser Ser Asp Leu Thr Gln Asp Pro Ala Val Ser Val Ala
                                  5
 Leu Gly Gln Arg Val Arg Ile Thr Cys Gln Gly Asp Asn Leu Glu Glu
                              20
 Tyr Phe Ala Ser Trp Tyr Arg Gln Arg Pro Gly Gln Ala Pro Val Leu
                          35
 Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Xaa Arg Xaa
                      50
                                          55
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Leu Leu Thr Ile Xaa Gly Ala
                  65
                                      70
 Gln Ala Glu Asp Xaa Ala Asp Tyr Tyr Cys Ser Xaa Arg Asp His Thr
             80
                                  85
 Asp Asn Arg Trp Val Phe Gly Gly Gly Thr Arg Leu Thr
                              100
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 Met Glu Ala Glu Phe Tyr Met Xaa Ile Leu Thr Cys Leu Ile Phe Arg
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                                         -10
Asn Ser Glu Gly Phe Gln Ile Xaa His Val Gln Lys Gln Gln Cys Leu
Phe Lys Asn Glu Lys Val Val Gly Ser Cys Asn Arg Thr Ile Gln
                             20
Asn Gln Gln Trp Met Trp Thr Glu Asp Glu Lys Leu Leu His Val Lys
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Ser Ala Leu Cys Leu Ala
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Cys Ser Ile
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<400> 1252
Met Ile Ser Asp Val Gln His Leu Phe Ile Tyr Leu Leu Ala Phe Cys
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-15
                                            -10
  Met Pro Ser Leu Glu Lys Cys Leu Tyr Gly Ser Leu Ala His Phe Phe
  -5
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  Phe Phe
  <210> 1253
  <211> 28
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  <213> Homo sapiens
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 Met Pro Leu Phe Arg Val Leu Phe Ser Xaa Thr Cys Ala Leu Xaa Gln
 -15 -10 -5
 Asp Phe Arg Met Gln Pro Cys Pro Pro Thr Pro Lys
             5
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 <210> 1254
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 <222> -24..-1
 <400> 1254
 Met Trp Tyr Val Glu Met Trp Val Ser Phe Phe Leu Leu Phe Tyr Val
              -20
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 Leu Leu Phe Arg Asn Leu Tyr Thr His Thr His His Thr Gly
 <210> 1255
<211> 54
 <212> PRT
 <213> Homo sapiens.
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 <222> -30..-1
 <400> 1255
 Met Ala Ala Arg Val Gly Ala Phe Leu Lys Asn Ala Trp Asp Lys Glu
                                            . -15
                   -25
                                       -20
 Pro Val Leu Val Val Ser Phe Val Val Gly Gly Leu Gly Cys Asn Xaa
                -10
                                   - 5
 Ala Pro Ile Glu Pro Leu Leu Gln Val Leu Arg His Asp Gln Gln Gly
                           10
 His Ala Leu Gln Leu Xaa
     20
 <210> 1256
 <211> 103
 <212> PRT
 <213> Homo sapiens
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 <222> -23..-1
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<211> 42

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<400> 1256
 Met Gln Ala Arg Arg Trp Glu Ser Trp Met Trp Thr Cys Val Ala Pro
             -20
                                 -15
                                                     -10
 Val Tyr Pro Ala Cys Ser Gly Arg Arg Ala Xaa Ala Val Xaa Gln Xaa
         -5
 Xaa Pro Arg Leu Gly Xaa Xaa Leu Pro Gly Pro Gly Xaa Glu His Leu
                     15
                                         20
 Ala His Val Cys Gly Leu Pro Ala Gly Glu Ala Gly Arg Gly Arg Gly
                 30
                                     35
 Val Glu Arg Pro Gln Glu Lys Arg Ala Asp Lys Ala Val Xaa Val Arg
                                 50
 Arg Gly Leu Gly Gly Ala Gly Leu Pro Gly Gly Asp Thr Pro Arg Gly
                             65
 Pro Pro Met Ser Thr Trp Pro
     75
 <210> 1257
 <211> 16
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
<222> -14..-1
<400> 1257
Met Phe Leu Phe Phe Gly Asn Ser Pro Cys Cys Gly Ala Thr Gly
                 -10
                                     -5
<210> 1258
<211> 40
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 1258
Met Gly Leu Ser His His Arg Val Ser Ala Pro Ser Ser Leu Ser Leu
                   -20
                                        -15
Ser Leu Ser Ala Ser Leu Ile Ile Ser Pro Ser Pro Ser Ala Ser Pro
               - 5
Ser Leu Leu Xaa Pro Pro Xaa Arg
    10
<210> 1259
<211> 32
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 1259
Met Phe Val Phe Leu Val Gly Thr Pro Cys Leu Ser Met Leu Leu Arg
           -20
                               -15
Leu Val Ser Asn Ser Arg Pro Pro Val Met Arg Pro Pro Arg Pro Gly
<210> 1260
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WO 99/53051 569 PCT/IB99/00712
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<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -33..-1

<400> 1260

Met Lys Phe Thr His Phe Lys Cys Thr Ile Arg Leu Leu Leu Tyr
-30 -25 -20

Leu Gln Asn Pro Val Thr Ile Thr Ile Leu Phe Leu Ile Val Ser Met
-15 -10 -5

Ala Leu Lys Ile Asn His Ile Pro Lys Gly
1 5

<210> 1261

<211> 42

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -14..-1

<400> 1261

Met Ser Cys Met Ser Leu Phe Pro Cys Cys Pro Ala Gln Ser Lys Asn
-10 -5

Tyr Met Leu Leu Phe Ile Ile Leu Leu Pro Thr Gln Phe Leu Tyr 5 10 15

Ser Lys Leu Val Thr Ile Cys Cys Cys Phe 20 25

<210> 1262

<211> 26

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -14..-1

<400> 1262

Met Leu Val Cys Cys Thr Ile Asn Ser Ser Phe Ala Leu Gly Ile Ser

Arg Asn Ala Ile Pro Leu Pro Ala Pro Gly

<210> 1263

<211> 69

<212> PRT

<213 > Homo sapiens

<220>

<221> SIGNAL

<222> -53..-1

<400> 1263

Met Gly Arg Gly Pro Gly Pro Leu Gln Glu Arg Ser Leu Phe Glu Xaa
-50 -45 -40

Lys Arg Gly Ala Pro Pro Ser Ser Asn Ile Glu Asp Phe His Gly Leu
-35 -30 -25

Leu Pro Lys Val Ile Pro Ile Cys Ala Leu Tyr Val Ile Cys Gln Phe
-20 -15 -10

<212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -13..-1

<211> 40

5 10 His Ser Thr Ile Leu Leu Cys Val

<210 > 1265 <211 > 37 <212 > PRT <213 > Homo sapiens

<220>
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<222> -26..-1

Ser Leu Phe Leu Ile Gln Leu Leu Ile Ser Phe Ser Glu Asn Gly Phe
-10 -5 1 5

Ile His Ser Pro Met

<210> 1266 <211> 21 <212> PRT <213> Homo sapiens

<220> .<221> SIGNAL <222> -14..-1

<210> 1267 <211> 42 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -33..-1

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 Met Phe His Gly Arg Val Met Ala Met Gly Xaa Leu Thr Lys His Leu
             -30
                                 -25
 Asn Leu Asn Ile Ser Ile Ser Leu Leu Leu Met Leu Xaa Xaa Tyr Trp
                             -10
 Ser Cys Trp Ile Lys Ser Pro Pro Xaa Met .
<210> 1268
 <211> 132
 <212> PRT
 <213> Homo sapiens
<220>
 <221> SIGNAL
 <222> -128..-1
<400> 1268
Met Leu Gly Arg Ser Ser Leu Leu Xaa Trp Lys Xaa Ser Pro Gly Ser
            -125
                     -120
                                                    -115
Lys Lys Leu Val Val Ala Thr Glu Lys Asn Val Ile Ala Ala Leu Asn
        -110
                            -105
                                                -100
Ser Arg Thr Gly Glu Ile Leu Trp Arg His Val Asp Lys Gly Thr Ala
    -95
                        -90
                                            -85
Glu Gly Ala Val Asp Ala Met Leu Leu His Gly Gln Asp Val Ile Thr
                    -75
                                        -70
Val Ser Asn Gly Gly Arg Ile Met Arg Ser Trp Glu Thr Asn Ile Gly
                -60
                                   -55
                                                        -50
Gly Leu Asn Trp Glu Ile Thr Leu Asp Ser Gly Ser Phe Gln Ala Leu
            -45
                                ~40
Gly Leu Val Gly Leu Gln Glu Ser Val Arg Tyr Ile Ala Val Leu Lys
        -30
                            -25
                                                -20
Lys Thr Thr Leu Ala Leu His His Leu Ser Ser Gly His Ser Ser Gly
    -15
                        -10 .
Trp Thr Ser Pro
1
<210> 1269
<211> 72
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -57..-1
<400> 1269
Met Ser Thr Thr Tyr Leu Asn Glu Asp Leu Lys Lys Lys Phe Ser Ala
        -55
                           -50
                                               -45
Val Ile Glu Gln Val Leu Phe Ala His Leu Ser Pro Leu His Val Trp
                       -35
                                            -30
Leu Gln Leu Arg Ser Leu Cys Glu Xaa Leu Thr Cys Ile Trp Val Arg
-25
                   -20
                                       -15
Phe Asn Phe Leu Ala Ser Ser Gln Ala Cys Ser Lys Cys Asn Ser Ser
               - 5
Phe Leu Ile Met Ser Ser Ser
       10
                           15
<210> 1270
<211> 80
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<213> Homo sapiens
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WO 99/53051 572 <220> <221> SIGNAL <222> -39..-1 <400> 1270 Met Ala Leu Ile Val Leu Gln Leu Thr Phe Gly Ile Gly Tyr Val Thr -35 -30 Leu Leu Gln Ile His Ser Ile Tyr Ser Gln Leu Ile Ile Leu Asp Leu -20 -15 Leu Val Pro Val Ile Gly Leu Ile Thr Glu Leu Pro Leu His Ile Arg - 5 Glu Thr Leu Leu Phe Thr Ser Ser Leu Ile Leu Thr Leu Asn Thr Val 15 20 Phe Val Leu Ala Val Lys Leu Lys Trp Phe Tyr Tyr Ser Thr Arg Tyr 30 35 <210> 1271 <211> 54 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -24..-1 <400> 1271 Met Arg Val Ala Gly Ala Ala Lys Leu Val Val Xaa Val Ala Xaa Phe -20 ~15 -10 -Leu Leu Thr Phe Tyr Val Ile Ser Gln Val Phe Glu Ile Lys Met Asp - - 5 1 Ala Ser Leu Gly Asn Leu Phe Ala Arg Ser Ala Leu Asp Thr Ala Ala Arg Ser Thr Lys Pro Pro <210> 1272 <211> 54 <2:12> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1 <400> 1272 Met His Thr Leu Val Phe Leu Ser Thr Arg Gln Val Leu Gln Cys Gln -10 -5 . Pro Ala Ala Cys Gln Ala Leu Pro Leu Leu Pro Arg Glu Leu Phe Pro 10 Leu Leu Phe Lys Val Ala Phe Met Xaa Lys Lys Thr Val Val Leu Arg 20 25 Xaa Leu Val His Thr Arq 35

<210> 1273 <211> 16 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14...1

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573
 <400> 1273
 Met Thr Val Val Ile Ser Cys Leu Val Gly Glu Cys Gly Ser Trp Lys
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                                    - 5
 <210> 1274
 <211> 72
 <212> PRT
 <213> Homo sapiens
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 <222> -47..-1
 <400> 1274
Met Cys Thr Leu Thr Asp Thr His Thr His Val Gln Val His Lys Ser
                     -40
Lys Pro Cys Gln Leu Leu Ser Pro Pro Pro Pro Xaa His Gly Pro Leu
                       -25
Leu Leu Pro Ile Phe Gly Leu Leu Val Pro Ser Gln Ile Phe Ser Ser
                   -10
                                       -5
Leu Leu Asn Ser Leu His Leu Gly Leu Pro Ser Phe Pro Lys Met Pro
                               10
Leu Met Ile Phe Leu Pro Arg Trp
 20
<210> 1275
<211> 78
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -63..-1
<400> 1275
Met Thr Leu Ile Leu Gly Glu Ser Ser Ser Gln Pro Gln Ile Ser Ile
                               -55
Phe Leu Trp Thr Lys Val Lys Asp Leu Phe Ser Leu Met Ile Thr Trp
       -45
                           -40
                                              -35
Thr Val Gln Met Lys Leu Thr Ser Met Trp Met Asn Leu Ile Pro Pro
 -30
                       -25
                                          -20
Met Lys Gln Ile Leu Xaa Ser Thr Leu Ala Met Lys Ile His Ser Gln
-15
                   -10
                                    -5
Gln Arg Phe Trp Pro Arg Val Arg Val Tyr Ser Arg Ile Tyr
                               10
<210> 1276
<211> 25
<212> PRT
<213> Homo sapiens
<220> -
<221> SIGNAL
<222> -19..-1
<400> 1276
Met Tyr Lys Glu Lys Leu Val Leu Phe Leu Leu Asn Leu Phe Gln Lys
               -15
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<210> 1277 <211> 88

Ile Glu Glu Glu Leu Phe Pro Asn

<222> -25..-1

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<212> PRT
  <213> Homo sapiens
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  <221> SIGNAL
 <222> -48..-1
 <400> 1277
 Met Asp Ser Val Pro Ala Thr Val Pro Ser Ile Ala Ala Thr Pro Gly
             -45
                                 -40
                                             -35
 Asp Pro Glu Leu Val Gly Pro Leu Ser Val Leu Tyr Ala Ala Phe Ile
         -30
                             -25
                                               -20
 Ala Lys Leu Leu Glu Leu Val Ala Thr Leu Pro Asp Asp Val Gln Pro
     -15
                         -10
                                            - 5
 Gly Pro Asp Phe Tyr Gly Xaa Xaa Trp Lys Leu Tyr Leu Ser Leu Pro
                                    10
 Ser Trp Glu Xaa Phe Val Cys His Phe Leu Met Glu Thr Val Leu Val
            20
 Val Lys Xaa Arg Val Tyr Xaa Val
         35
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 <211> 39
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -18:.-1
 <400> 1278
 Met Ala Ala Tyr Phe Ala Val Trp Ala Ser Val Ala Ser Pro Ala Ser
            -15
                               -10
                                                    - 5
 Ile Cys Cys Gly Xaa Trp Leu Thr Gly Leu Val Arg His Glu Arg Ile
      1
                       5
                                           10
Glu Ala Pro Trp Ala Arg Gly
                    20
<210> 1279
<211> 34
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -29..-1
<400> 1279
Met Lys Thr Gln Phe Leu Ser Trp Gly Lys Phe Ser Phe Cys Phe Gly
               -25
                                    -20
Ile Leu Leu Ile Leu Gln Leu Leu Lys Xaa Ser Leu Lys Lys Cys Arg
His Gly
  5
<210> 1280
<211> 40
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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Met Leu Pro Ala Val Ala Val Ser Glu Pro Val Val Leu Arg Phe Ile
 -25
                      -20
                                  -15
  Leu Pro Ser Ser Trp Asp Cys Arg Cys Ala Pro Pro Leu Leu Thr Gly
                  - 5
  Phe Cys Ile Phe Trp Xaa Glu Thr
  <210> 1281
  <211> 60
  <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -33..-1
 <400> 1281
 Met Asp Pro Ala Ala Pro Trp Leu Phe Trp Glu Ala Ala Ala Pro Ala
             -30
                                 -25
 Leu Lys Arg Pro Trp Leu Leu Met Val Ala Pro Arg Leu Pro Ala Gly
         - 15
                             -1.0
 Ala Arg Asp Ser Gly Gln Phe Pro Arg Lys Gly Gln Ala Gly Ser Pro
                                         10
 Ser Arg Gly Arg Val Arg Lys Leu Gly Gly Ala Val
 <210> 1282
 <211> 38
 <212> PRT
 <213> Homo sapiens
<220>
<221> SIGNAL
<222> -31..-1
<400> 1282
Met Lys Met Ser Thr Pro Ser Pro Leu Ser Lys Lys Val Leu Arg Asn
                        -25
                                            -20
Gln Val Ser Arg Leu Xaa Ala Leu Leu Ser Pro Tyr Ala Phe Thr Leu
                    -10
Xaa Arg Leu Ala Ser Gly
            5
<210> 1283
<211> 58
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400>, 1283
Met Arg Arg Phe Leu Leu Tyr Ala Thr Gln Gln Gly Gln Ala Lys
                    -10
                                        ~5
Ala Ile Ala Glu Glu Met Cys Xaa Gln Ala Val Val His Gly Phe Ser
                                10
Ala Asp Leu His Cys Ile Ser Glu Ser Asp Lys Val Ser Val Ile Gln
Asn Thr Pro Thr Phe Ala Thr Gly Gly Arg
    35
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<211> 41
 <212> PRT
 <213> Homo sapiens
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 <222> -27..-1
 <400> 1284
 Met Leu Ile Asp Ile Trp Ser Met Val Leu Arg Glu Asn Leu Phe Val
        -25
                             -20
                                                 -15
 Asn Leu Asn Leu Cys Phe Ala Tyr Thr Phe Ala Leu Tyr Ser Cys Pro
                         -5
                                            1
 Ala Pro Thr Arg Cys Pro Arg Pro Ser
                10
 <210> 1285
 <211> 73
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -18..-1
 <400> 1285
Met Leu Ser Cys Pro Trp Phe Pro Leu Ser Cys Ser Pro Ser Leu Pro
            -15
                               -10
Leu Ser Ile Pro Asp Cys Leu Pro Ala Phe Leu Trp Pro Leu Gly Ile
      1
Pro Trp Pro Asp Gly Glu Gly Leu Arg Pro Ser Arg Leu Leu Arg Thr
15
                    20
                                     25
Arg Glu Asn Ile Thr Pro Leu Ser Leu Phe Ala Met Leu Ser Gly Arg
                35
                                                         45
Glu Gly Ala Pro Leu Leu Val Pro Leu
            50
<210> 1286
<211> 20
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -13..-1
<400> 1286
Met Val Val Val Ser Phe Leu Ala Ser Ser Ser Leu Pro Ala Glu Thr
           -10
                                                    1
Pro Lys Gln Gly
    5
<210> 1287
<211> 145
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -107..-1
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 Met Gly Xaa Leu Ala Leu Xaa Ala Trp Leu Gln Pro Arg Tyr Arg Lys
                              -100
 Asn Ala Tyr Leu Phe Ile Tyr Tyr Leu Ile Gln Phe Cys Gly Xaa Ser
                          -85
 Trp Ile Phe Ala Asn Met Thr Val Arg Phe Phe Ser Phe Gly Lys Asp
                     -70
 Ser Met Val Asp Thr Phe Tyr Ala Ile Gly Leu Val Met Arg Leu Cys
                 -55
                                     -50
 Gln Ser Val Ser Leu Leu Glu Leu Leu His Ile Tyr Val Gly Ile Glu
             -40
                                 -35
 Ser Asn His Leu Leu Pro Arg Phe Leu Gln Leu Thr Glu Arg Ile Ile
         -25
                             -20
                                                  -15
 Ile Leu Phe Val Val Ile Thr Ser Arg Arg Gly Ser Pro Thr Arg Asn
                         - 5
Met Trp Cys Val Cys Tyr Ser Ser Leu Asp Leu Trp Ile Trp Leu Xaa
                .10
                                     15
 Thr Leu Ile Ala Xaa Xaa Ser Val Ile Gly Ile Ser Tyr Ala Val Leu
             25 .
                                 30
 Thr
 <210> 1288
 <211> 21
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<213> Homo sapiens
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<222> -18..-1
<400> 1288
Met Asp Thr Phe Pro Ser Leu Thr Leu Thr Ala Leu Leu Val Pro Ser
            -15
                                 -10
Arg Val Gln Pro Gln
<210> 1289
<211> 84
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 1289
Met Gly Leu Thr Lys Gln Tyr Leu Arg Tyr Val Ala Ser Ala Val Phe
                    -15
                                         -10
Gly Val Ile Gly Ser Gln Lys Gly Asn Ile Val Phe Val Thr Leu Arg
Gly Glu Lys Gly Arg Tyr Val Ala Val Pro Ala Cys Glu His Val Phe
Ile Xaa Asp Leu Arg Lys Gly Glu Lys Ile Leu Ile Leu Gln Gly Leu
                        .35
                                             40
Lys Gln Glu Val Thr Cys Leu Cys Pro Ser Pro Asp Gly Leu His Leu
45
                    50
Ala Val Gly Tyr
<210> 1290
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<213> Homo sapiens

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<220> <221> SIGNAL <222> -24..-1 <400> 1290 Met Met Gly Ile Phe Leu Val Tyr Val Gly Phe Val Phe Phe Ser Val -20 -15 -10 Leu Tyr Val Gln Gln Gly Leu Ser Ser Gln Ala <210> 1291 <211> 47 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1. <400> 1291 Met Ser Leu Gly Leu His Ser Asn Ser Trp Val Leu Asp Pro Ala Leu -20 -15 -10 Leu Leu Thr Cys Leu Thr Phe Pro Ile Tyr Lys Leu Leu Trp Val Arg 1 Gly Gly Thr Arg Xaa Thr Leu Xaa Ala Leu His Ser Ala Arg Thr 15 <210> 1292 <211> 68 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1 <400> 1292 Met Ala Ala Asn Ser Ser Gly Gln Gly Phe Gln Asn Lys Asn Arg Val -55 -50 Ala Ile Leu Ala Glu Leu Thr Lys Arg Lys Glu Asn Tyr Leu Cys Arg -40 -35 -30 Thr Ser Leu Gln Gln Ile Ile Leu Glu Leu Gly Ile Asp Thr Ile Met -25 -20 -15 Trp Val Xaa Cys Xaa Phe Cys Phe Val Leu Phe Cys Phe Glu Thr Glu -10 -5 1 Ser Arg Pro Val <210> 1293 <211> 138 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -35..-1 <400> 1293

Met Ser Ala Gly Ser Ala Thr His Pro Gly Ala Gly Gly Arg Arg Ser -35 - 25 - 25 - 20

Lys Trp Asp Gln Pro Ala Pro Ala Pro Leu Leu Phe Leu Pro Pro Ala -15 - 10 - 5

Ala Pro Gly Gly Glu Val Thr Ser Ser Gly Gly Ser Pro Gly Xaa Thr

```
Thr Ala Ala Pro Ser Gly Ala Leu Asp Ala Ala Ala Ala Val Ala Ala
                            20
   Lys Ile Asn Ala Met Leu Met Ala Lys Gly Lys Leu Lys Pro Thr Gln
                       35 -
                                           40
   Xaa Ala Ser Glu Lys Leu Gln Ala Pro Gly Lys Gly Leu Thr Ser Asn
                   50
                                       55
   Lys Ser Lys Asp Asp Leu Val Val Ala Glu Val Glu Ile Asn Asp Val
                                   70
   Pro Leu Thr Cys Arg Asn Leu Leu Thr Arg Gly Gln Xaa Gln Asp Glu
                               85
   Ile Ser Arg Leu Ser Gly Ala Ala Val Ser
   95
                           100
   <210> 1294
   <211> 58
   <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -21..-1
  <400> 1294
  Met Ser Pro Leu Asp Gln Ala Val Ile Arg Ala Val Cys Leu Ser Gly
                          -15
                                              -10
  Gly Ser Cys Trp Gly Gly Val Arg Cys Leu Val Arg Gly Gly Pro Asn
  Ile Gly Pro Ala Ala Gln Leu Leu Gly Gly Ile Pro Leu Cys Trp Pro
  Pro Ala Val Thr Ala Gly Glu Val Lys Leu
        30
  <210> 1295
  <211> 19
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -15..-1
  <400> 1295
 Met Asn Ser Phe His Phe Ile Xaa Phe Leu Pro Phe Pro Trp Ala Glu
 -15
                     -10
                                          - 5
 Xaa Ala Gln
 <210> 1296
 <211> 35
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -29..-1
<400> 1296
 Met Gly Trp His Ser His Ser Ser Gln Gly Val Xaa Ala Met Pro Leu
                                     -20
 Leu Leu Ser Thr His Thr Trp Thr Asp Thr Ala Leu Ala Phe Ser Thr
                                 -5
 His Thr His
     5
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<210> 1297
   <211> 35
   <212> PRT
   <213> Homo sapiens
   <220>
   <221> SIGNAL
   <222> -22..-1
   <400> 1297
  Met Xaa Ala Val Arg Asn Ala Gly Ser Trp Phe Leu Arg Ser Trp Thr
                               -15
  Trp Pro Gln Thr Ala Gly Arg Val Val Ala Arg Xaa Pro Ala Gly Thr
                                                   -10
   - 5
                           1
                                           5
  Ile Cys Thr
  <210> 1298
  <211> 23
  <212> PRT
  <213> Homo sapiens
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  <221> SIGNAL
  <222> -15..-1
  <400> 1298
 Met Cys Ala Leu Phe Ile Leu Val Ser Ile Ser Leu Phe Tyr Ala Leu
                     -10
                                          - 5
 Phe Ile Ser Pro Ser Ile Gln
              5
 <210> 1299
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 <222> -53..-1
 <400> 1299
 Met Tyr Leu Val Cys Thr Thr Cys Thr Trp Cys Val Phe Ser Glu Met
                                -45
Phe Val His Gly Leu Asn Ile Thr Gln Leu Val Leu Ser Gln Leu Asp
        -35
                             -30
                                                 -25
Tyr Phe Phe His Ser Asn Leu Thr Asn Leu Val Leu Tyr Phe Leu Val
                        -15
His Leu Leu Phe Ser Leu Ser Leu Phe Met Pro Leu Thr
-5
                    1
<210> 1300
<211> 138
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -78..-1
<400> 1300
Met Lys Leu Lys Leu Tyr Leu Cys Ile Leu Gly Pro Trp Gly Cys Xaa
           -75
                                -70
                                                    -65
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Xaa Lys Val Pro Leu Ile Gly Phe Leu Lys Arg Ile Xaa Xaa Tyr Xaa
                             -55
  Leu Thr Val Leu Lys Pro Xaa Ser Leu Xaa Ser Xaa Ser Ala Gly Leu
                          -40
                                             -35
  Val Pro Ser Glu Asp Ser Lys Lys Glu Ser Val Ser Cys Leu Ser Pro
                -25
                                         -20
  Arg Phe Trp Trp Leu Gly Ser Leu Xaa Val Thr Trp Leu Ile His
                                                            -15
                  -10
                                     -5
  Ala Ser Leu Gln Ser Leu Ser Pro Phe Ser His Ala Ile Phe Ser Cys
                             10
  Val Ser Val Phe Ser Phe Ala Tyr Lys Asp Thr Ser His Ile Glu Leu
      20
                         25
                                             30
  Gly Pro Ala Leu Ile Thr Ser Ser Gln Leu Pro Leu Gln Gly Thr Asn
  35
                    40
  Phe Gln Ile Met Ser His Ser His Val Ala
                 55
 <210> 1301
  <211> 35
  <212> PRT
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 <222> -33..-1
 <400> 1301
 Met Asn Glu Lys Lys Leu Leu Gly Thr Glu Gln Lys Gln Lys Lys
            -30
                                .-25
                                                   -20
 Arg Met Gly Asn Leu Lys Leu Leu Phe Leu Ile Leu Ile Leu Ile Ala
     -15
 Gly Tyr Arg
 . 1
 <210> 1302
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 <222> -27..-1
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Met Gly Leu Gln Ser Leu Thr Leu Pro Val Ser Cys Ser Pro Ser Ala
    -25
                         -20
                                 -15
Leu Met Leu Pro Leu Gly Cys Ala Val Arg Thr Arg Met Leu
   -10
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Trp Ile Leu Thr Thr Leu Glu Ser Leu Ala Gly Ser Val Xaa Ser Glu
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Gln Asp Leu Ser Ala Tyr
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  Met Thr Cys Met Leu Ala Cys Arg Cys Ser Leu Xaa Gly Pro Gln Asp
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  Phe Arg Phe Cys Ser Val Phe Ser Leu Leu Leu Lys Leu Gly Asn Phe
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                         -25
  Tyr Phe Ser Phe Xaa Xaa Cys Leu Phe Leu Xaa Leu Xaa Xaa Ser Glu
  -15
          -10
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  Met Glu Ser His Ser Phe Ser
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 Met Glu Asp Val Glu Ala Arg Phe Ala His Leu Leu Gln Pro Ile Arg
                    -60
                                -55
 Asp Leu Thr Lys Asn Trp Glu Val Asp Val Ala Ala Gln Leu Gly Glu
                -45
                                   -40
 Tyr Leu Glu Glu Leu Asp Gln Ile Cys Ile Ser Phe Asp Glu Gly Lys
            -30
                                -25
 Thr Thr Met Asn Phe Ile Glu Ala Ala Leu Leu Ile His Gly Ser Ala
                            -10
 Cys Val Tyr Ser Lys Lys Val Glu Tyr Leu Tyr Ser Leu Val Tyr Gln
   1
                   5
                                       10
Ala Leu Asp Phe Ile Ser Gly Lys Arg Arg Ala Lys Gln Leu Ser Ser
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Val Gln Glu Asp Arg Ala Asn Gly Val Ala Ala Pro Gly Ser Pro Gly
Gly
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Met Phe Val Ser Tyr Leu Ile Leu Thr Leu Leu His Val Gln Thr Ala
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Val Leu Ala Arg
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  Met Pro Glu Ala Ala Leu Phe Leu Phe Phe Leu Phe Ile Phe Leu Leu
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  Tyr Phe Lys Phe Trp Gly Thr Cys Ala Glu Arg Ala Gly Leu Leu His
                  - 5
                                      1
                                                      5
  Arg Tyr Thr Arg Ala Met Glu Val Cys Cys Thr His Gln Pro Ser Ser
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  Thr Leu Gly Ile Ser Pro Asn Ala Leu Leu Pro Leu
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  Met Arg Met Gly Thr Arg Ala Ser Pro Pro Leu Cys Met His Leu Ser
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  Ile His Pro Xaa Xaa Cys Ala Cys Ile Cys Pro Ser Ile Gln
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 Met Tyr Pro Arg Val Trp Gly Cys Phe Gln Leu Leu His Xaa Leu Xaa
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 Xaa Thr Arg Thr Thr Gly Lys Xaa Val Cys Val Cys Val Cys
                     -15
                                         -10
 Val Cys Val Cys Val Cys
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Met Ala Ala Val Val Leu Ala Ala Thr Arg Leu Leu Arg Gly Ser Gly
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                                    - 5
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584
   Ser Trp Gly Cys Ser Arg Leu Arg Phe Gly Pro Pro Ala Tyr Arg Arg
                                10
   Phe Ser Ser Gly Gly Ala Tyr Pro Asn Ile Pro Leu Ser Ser Pro Leu
                            25
   Pro Gly Val Pro Lys Pro Val Phe Ala Thr Val Asp Gly Gln Glu Lys
                        40
   Phe Glu Thr Lys Val Thr Thr Leu Asp Asn Gly Leu Arg Val Ala Ser'
                    55
                                        60
   Gln Asn Lys Phe Gly Gln Phe Cys Thr Val Gly Ile Leu Ile Asn Ser
   Gly Ser Arg Tyr
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  Met Tyr Cys Leu Xaa Cys Val Glu Lys Ile Ala Lys Ala Leu Tyr Leu
   -25
                       -20
                                           -15
  Ser Leu Asn Leu Tyr Phe Ala Asn Ser Leu Tyr Tyr Met Cys Val Cys
  Ser Tyr Ile Tyr Phe Tyr Leu Xaa Ile Tyr Xaa Tyr Xaa Leu Ile Lys
                              15
  Xaa Xaa Ser Tyr Tyr Val Ala Gln Thr Gly Leu
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 Met Cys Gln Leu Arg Arg Gly Leu Gly Lys Arg Pro Leu Ser Glu Ala
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                                      -20
 Ser Ala Val Phe Leu Thr Ala Val Phe Ser Ser His Ser Trp Leu Val
              -10
 Gly Pro Arg Tyr
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 Met Ser Val Arg Ser Thr Trp Cys Arg Ala Gln Phe Asn Ser Trp Val
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 Ser Leu Leu Thr Phe Cys Leu Ile Asp Leu Ser Asn Val Asp Ser Gly
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Xaa
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Ile Ser Trp Thr Leu Ser Val Ser Ser His Gly Pro Val Cys Gly Cys
15 20 25
Trp Ala Phe Arg Phe His Asn Pro His Gly Leu Leu Ser Ser Arg Ser

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WO 99/53051
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  His Leu Ser Xaa Trp Leu His Ser Ala Gly
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  Met Val Val Ser Ala Phe Ile Tyr Leu Phe Phe Glu Thr Gly Ser
                             -15
  Pro Ser Val Ala Gln Ser Gly Val Gln Trp Cys Asp Leu Gly Leu Leu
 Gln Pro Pro Pro Gly Phe Lys Arg Phe Ser Cys Leu Ser Leu Leu
                 15
                                     20
 Gly Xaa Xaa Asp Cys Arg Arg Ala Pro Pro Gly
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 Met Phe Val Ser Xaa Thr Xaa Phe Phe Phe Xaa Leu Xaa Phe Leu Gly
                 -20
                                     -15
Met Phe Leu Ser Gly Met Val Ala Gln Ile Asp Ala Asn Trp Asn Phe
Leu Asp Phe Ala Tyr His Phe Thr Val Phe Val Phe Tyr Phe Gly Ala
                         15
                                             20
Phe Leu Leu Glu Ala Ala Ala Thr Ser Leu His Asp Leu His Cys Asn
                    30
                                         35
Thr Thr Ile Thr Xaa Gln Pro Leu Leu Ser Asp Asn Gln Tyr Asn Ile
                                    50
Asn Val Ala Ala Ser Ile Phe Ala Phe Met Thr Thr Ala Cys Tyr Gly
            60
Cys Ser Leu Gly Leu Ala Leu
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Met Ser Ser Glu Ile Phe Xaa Xaa Xaa Ile Ala Tyr Ala Xaa Tyr
                       -20
                                           -15
Leu Leu Val Gly Leu Phe Pro Leu Lys Cys His Xaa Ser Xaa Phe Ser
                    - 5
Lys Xaa Gln Ile Ser Ser Phe Val Glu
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 Met Ala Ala Ser Ser Leu Thr Val Thr Leu Gly Arg Leu Ala Ser Ala
             -15
                                  -10
 Cys Ser His Ser Ile Leu Arg Pro Ser Gly Pro Gly Ala Ala Ser Leu
         1
 Trp Ser Ala Ser Arg Arg Phe Asn Ser Gln Ser Thr Ser Tyr Leu Pro
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                     20
                                          25
 Gly Tyr Val Xaa Lys Thr Ser Leu Ser Ser Pro Pro Trp Pro Arg
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 Met Leu Ile Ala Ala Cys Ile Cys Ser Cys Leu Phe Phe Ser Gln Tyr
            -15
                                 -10
Leu Xaa Xaa Ser Asn Pro Ala Ala
        1
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Met Lys Cys Trp Val Leu Ser Tyr Met Trp Gln Ser Ala Ser Leu Gly
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                                            - 5
Phe Ser Asn Arg Ile Lys Ser Xaa Leu Arg Pro Pro Ala Gly
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Met Ser Val Gly Leu Cys Phe Leu Ile Trp Gln Met Gly Ile Met Leu

-60

-65

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588
   Leu Pro Arg Glu Cys Trp Lys Val Lys Asp Ser Lys Lys Tyr Lys Ser
               -50
                        -45
   Cys Arg Glu Ser Val Leu Pro Ala Gln Ala Cys Thr Gly Glu Ser Pro
          - 35
                              -30
   Val Leu Ser Gly Val Arg Val Leu Gly Ile Arg Leu Ser Cys Val Leu
      -20
                      -15
  Ser His Leu Gln Ala Trp Asp Ser Trp Asp Asn Gln Lys Val Cys Tyr
                      1
  Leu Gly Ala Pro Cys Phe Gly Lys Arg Leu Ser Pro Thr Thr Trp Leu
              15
                                  20
  Thr Phe Trp Val Gly
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  <221> SIGNAL
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  <400> 1324
 Met Phe Ala Phe Leu Ala Gly Cys Ser Gly Ser Cys Leu Trp Ser Arg
                 -10
                                     - 5
 His Phe Gly Arg Leu Arg Arg Ala Ala Pro Leu Ser Pro Glu Phe Glu
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 Thr Gly Leu Gly Asn Met Val Glu Pro Gln Trp
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Met Pro Thr Tyr Phe Leu Phe Val Pro His Leu Ile Ser Cys Asn Trp
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 Cys Glu Pro Arg Gly Asn Asn Pro Gln Ile Pro Leu Leu Ala Ile His
 Thr Arg Lys Lys Asn Gln His Phe Ile Thr
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<211> 59
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Met Leu Trp Thr Ser Phe Gln Asn Pro Leu Gln Val Val Leu Leu Thr
       -25
                           -20
Ser Val Ser Leu Xaa Xaa Xaa Xaa Xaa Gly Ser Val Arg Ile Xaa
                       - 5
Leu Ser His Trp Ser Ser Ser Ala Phe Phe Phe Leu Ile Xaa Xaa
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<210> 1328 <211> 40 <212> PRT <213> Homo sapiens <220>

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  Met Gln Leu Gln Val Leu Gly Arg Pro Gln Gly Ala Pro Gln Leu Ala
                           -25
                                               -20
  Pro Gln Ala Leu Ala Leu Thr Xaa Thr Leu Leu Pro Ala Pro Gly Glu
                      -10
                                           - 5
  His Asp Ser Pro Met Xaa Ile Gly Gln Phe Pro Xaa Asn Pro Pro Ser
                                  10
                                                       15
  Glu His Pro Gly Ala Ser Pro Arg Arg Xaa Xaa Thr Gly Trp Xaa Pro
                              25
  Gln Ser Trp Asp Arg Arg Val Ser Pro Ala Glu Ala Glu Thr Arg Arg
      35
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 Met Gly Val Tyr Thr Cys Pro Ile Phe Val His Tyr Tyr Glu Asn His
                         -35
                                              -30
 Gly Pro Thr Pro Ser Phe Xaa Ala Phe Ile Ser Phe His Leu Phe Thr
 -25
                     -20
                                          -15
 Leu Gly Phe Leu Cys Ser Leu Cys Pro His Pro His Gly
                 -5
 <210> 1332
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Met Lys Lys Ser Val Ser Cys Cys Ser Ser Leu Trp Val Ser Leu Ser
 -15
                        -10
Lys Asp Glu Asn Ala Glu Met
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Met Leu Leu Pro Leu Ala Met Ala Gly Arg Cys Tyr Thr Ala Lys His
                   -25
Ser Thr Val Leu Leu Ser Gly Ser Pro Arg Ala Val Val Ser Ala Val
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<400> 1335 Leu Trp Ile Val Cys Cys Leu His Leu Asp Ser Leu Ile Ser Xaa Lys Tyr Pro Leu His Ala Ile Arg Arg Tyr Leu Ser Thr Leu Arg Asn Gln 15 20 Arg Ala Glu Glu Gln Val Ala Arg Phe Gln Lys Ile Pro Asn Gly Glu 30 35 Asn Glu Thr Met Ile Pro Val Leu Thr Ser Lys Lys Ala Ser Glu Leu 45 50 Pro Val Ser Glu Val Ala Ser Ile Leu Gln Ala Asp Leu Gln Asn Gly 60 65 Leu Lys Gln Cys Glu 75

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Phe Phe Phe Phe

<210> 1337 <211> 45 <212> PRT <213> Homo sapiens

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                                     -10
  Cys Trp Cys Leu Ser Phe Pro Thr Ser Ser Phe Thr Glu Ser Val Met
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 Arg Ser Leu Gly Glu Cys Pro Arg Lys Arg Trp Gly Gly
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 Met Xaa Lys Leu Xaa Ser Asn Pro Ser Glu Lys Gly Thr Lys Pro Pro
                 -80
                                     -75
                                                         -70
 Ser Val Glu Asp Gly Phe Gln Thr Val Pro Leu Ile Thr Pro Leu Glu
            -65
                                 -60
                                                     -55
 Val Asn His Leu Gln Leu Pro Ala Pro Glu Lys Val Ile Val Lys Thr
        -50
                             -45
 Arg Thr Glu Tyr Gln Pro Glu Gln Lys Asn Lys Gly Lys Phe Arg Val
                         -30
                                             -25
 Pro Lys Ile Ala Glu Phe Thr Val Thr Ile Leu Val Ser Leu Ala Leu
                    -15
                                         -10
Ala Phe Leu Ala Cys Ile Val Phe Leu Val Val Tyr Lys Ala Phe Thr
                1
Tyr Asp His Ser Cys Pro Glu Asp Ser Ser Xaa Ser Thr Gly
                             20
<210> 1339
<211> 51
<212> PRT
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<400> 1339
Met Phe Xaa Ala Ala Gly Val Glu Val Leu Ser Leu Leu Phe Xaa
                        -15
                                            -10
Cys Ile Tyr Trp Gly Gln Tyr Ala Thr Asp Gly Ile Gly Asn Glu Ser
Val Lys Ile Leu Ala Lys Leu Leu Phe Ser Ser Phe Leu Ile Phe
Leu Leu Met
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   <221> SIGNAL
  <222> -26..-1
  <400> 1340
  Met Leu Thr Gly Arg Phe Leu Gly Gly Ser Gln Gly Phe Phe Leu Ser
                         -20
                                             -15
  Phe Leu Ser Phe Phe Phe Phe Ser Phe Phe Leu Phe Leu Xaa Phe Phe
 Phe Phe Phe
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  <211> 41
  <212> PRT
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  <400> 1341
 Met Phe Ile Xaa Xaa Xaa Met Lys Gln Xaa Phe His Ile Ile Asp Phe
          -25
                                -20
 Val Phe Met Ser Lys Leu Leu Phe Ser Phe Ser Phe Leu Xaa Lys
  -10
                             - 5
 Ala Arg Met Xaa Thr Ala Ala Pro Gly
 <210> 1342
 <211> 37
 <212> PRT
 <213> Homo sapiens
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 <222> -18..-1
<400> 1342
Met Val Thr Pro Val His Ile Leu Thr Ala Val Leu Pro Leu Val Ser
            -15
                              -10
His Gln Gln Asn His Leu Gly Gly Arg Phe Ala Ser Leu Gly Ser Ser
                                            10
Gly Ile Arg His Gly
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<210> 1343
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<400> 1343
Met Leu Ile Leu His Leu Ala Thr Leu Leu Asn Leu Phe Ile Ser Ser
-15
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-10

Asn Ser Phe

<213> Homo sapiens

. <210> 1344 <211> 27 <212> PRT

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WO 99/53051
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  <221> SIGNAL
  <222> -15..-1
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                      -10
                                          -5
  Arg Ser Ile Ile Trp Lys Ser Gly Arg Gln Gly
                                  10
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  <211> 36
  <212> PRT
  <213> Homo sapiens
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  <221> SIGNAL
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 <400> 1345
 Met Glu Thr Trp Asn Gly Thr Ser Ile Ile Val Ala His Leu Xaa Ser '
                  -25
                                              -20
 Phe Ser Phe Leu Ser Phe Leu Ser Phe Arg Ser Pro Leu Cys His
                     -10
                                          -5
 His Pro Leu Gly
 <210> 1346
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Met Gln Phe Leu Ser Leu Ile Phe Ala Ser Cys Ser Ser Thr Thr Pro
                -10
                                    -5
Leu Pro Leu Xaa Gln Cys Cys Thr Leu Pro
        5
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Met Val Thr Ser Lys Ser Arg Gly Pro Xaa Val Gln Thr Leu Gly His
            -50
                               -45
Ala Gly Asn Leu Arg Ser Leu Arg Glu Trp Pro Asp Leu Cys Cys Leu
        +35
                            -30
Arg Leu Phe Val Pro Asp His Thr Val Leu Ala Leu Val Cys His Ser
    -20
                        -15
                                            -10
Ala Ser Ile Ser Val Phe Pro Ser Gln Val Thr Cys Arg Leu Pro Arg
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1

15

Pro His Pro Asn

Thr Gly Ser His Pro Ile Cys Val Ile Ser Gln Gly Ala Phe His Asp

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<400> 1348
Met Pro Arg Ser Ile Asp Xaa Lys Ala Leu Ile Trp Thr Val Arg Leu
     -25
                       -20
                                              -15
Val Val Leu Phe Ala Ser Pro Xaa Val Arg Pro Ala Ser Ser Met Ser
   -10
                    - 5
                                          1
Ser Arg Leu Leu Pro Xaa Leu His Tyr Ser Asp Trp Thr Cys Trp
           10
                                  15
Leu Pro Glu Arg Arg
  . 25
<210> 1349
<211> 91
<212> PRT
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<222> -54..-1
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Met Thr Ser Leu Leu Thr Thr Pro Ser Pro Arg Glu Glu Leu Met Thr
              -50
                                  -45
Thr Pro Ile Leu Gln Pro Thr Glu Ala Leu Ser Pro Glu Asp Gly Ala
           -35
                              -30
Ser Thr Ala Leu Ile Ala Val Val Ile Thr Val Val Phe Leu Thr Leu
       -20
                          -15
                                              -10
Leu Ser Val Val Ile Leu Ile Phe Phe Tyr Leu Tyr Lys Asn Lys Gly
                      1
Ser Tyr Val Xaa Tyr Glu Pro Thr Glu Gly Glu Pro Ser Ala Ile Val
              15
Gln Met Glu Xaa Xaa Leu Ala Lys Gly Ser Glu
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<222> -23..-1
<400> 1351
Met Ala Gln Leu Ile Met Trp Leu Lys Asn Gln Leu Ile Leu Leu Gly
            -20
                                -15
Ile Phe Arg Gly Ile Arg His Gln Ile Tyr Leu Ile Arg Thr Leu Gln
        - 5
Ile Arg Gln Trp
10
<210> 1352
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<212> PRT
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<222> -30..-1
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Met Gly Pro Val Pro Gly Ala Ala Gly Val Xaa Pro Xaa Xaa Gly
-30
                    -25
                                      -20
                                                          -15
Glu Leu Ala Xaa Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Val Ser
           -10
                                    -5
Ile Thr Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly
                           10
Pro Glu Trp Ile Gly Xaa Ile Asp His Ser Gly Asp Thr Asp Tyr Asn
                        25
                                           30
Pro Ser Leu Gln Ser Arg Val Thr Leu Ser Val Asp Thr Ser Lys Asn
                   40
                                        45
Gln Phe Ser Leu Arg Leu Leu Ser Val Ser Ala
                55
<210> 1353
<211> 39
<212> PRT
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<222> -36..-1
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Met Trp Phe Gln Thr Arg Ser Cys Gly His His Asp Pro Val Gly Ile
   -35
                       -30
                                            -25
Thr Gly Val Thr Lys Val Ile Leu Pro Leu Phe Leu Cys Pro Leu Gly
                   -15
                                       -10
Met Val Glu Thr Ser Phe Gly
<210> 1354
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<212> PRT
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<222> -109..-1

<400> 1354

Met Ser Tyr Val Val Thr Lys Thr Lys Ala Ile Asn Gly Lys Tyr His

Arg Phe Leu Gly Arg His Phe Pro Arg Phe Tyr Val Leu Tyr Thr Ile'
-90 -85 -80

Phe Met Lys Gly Leu Gln Met Leu Trp Ala Asp Ala Lys Lys Ala Arg
-75 -70 -65

Arg Ile Lys Thr Asn Met Trp Lys His Asn Ile Lys Phe His Gln Leu
-60 -55 -50

Pro Tyr Arg Glu Met Glu His Leu Arg Gln Phe Arg Gln Asp Val Thr
-45 -35 -30

Lys Cys Leu Phe Leu Gly Ile Ile Ser Ile Pro Pro Phe Ala Asn Tyr
-25
-20

Leu Val Phe Leu Leu Met Tyr Leu Phe Pro Arg Gln Leu Leu Ile Arg

<210> 1355

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -19..-1

<400> 1355

Met Tyr Asn Tyr Tyr Phe Leu Ser Leu Pro Ser Phe Leu Cys Thr Cys
-15 -10 -5

Cys Gln Phe Phe Pro His Asp Pro Ile Ser Ser Gln Tyr Ser Ser Pro

Gln Gly Lys Pro Cys Gln Val Thr Tyr Lys Phe Leu Phe Ile Leu Leu
15 20 25

Gly His Val Tyr Pro Arg Asp Gly Gly 30 35

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Met Gln Gly Gly Asn Ser Gly Val Arg Lys Arg Glu Glu Glu Gly Asp
-75
-70
-65

Gly Ala Gly Ala Val Ala Ala Pro Pro Ala Ile Asp Phe Pro Ala Glu
-60 -55 -50

Gly Pro Asp Pro Glu Tyr Asp Glu Ser Asp Val Pro Ala Xaa Ile Gln
-45 -40 -35

Val Leu Lys Glu Pro Leu Gln Gln Pro Thr Phe Pro Phe Ala Val Ala
-30
-25
-20

Asn Gln Leu Leu Leu Val Ser Leu Leu Glu His Leu Ser His Val His
-15
-10
-5
1
Glu

<210> 1357

<211> 21

<212> PRT

<213> Homo sapiens

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 Met Val Phe Tyr Cys Phe Ala Leu Cys Ile Ile Leu Ile Cys Val Met
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 Ser Cys Arg His Leu
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Met Leu Trp Glu Thr Asp Leu Ser Thr Asn Lys Thr Pro Val Ser Cys
           -40
                               -35
                                                   -30
Thr Ala Gly Ser Ala Cys Ala Leu Ser Leu Leu Gln Phe Pro Val Leu
    -25
                           -20
                                               -15
Ile Thr Gln Leu Cys Leu Gly Lys Gly Gln Ser Glu Pro Ile Gly Pro
                    -5
                                           1
Leu Gln Asp Phe Val Ser Leu Glu Ser Thr Ser His Phe Tyr Ser Phe
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Phe
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Met Thr Arg Arg Arg Thr Ser Leu Trp Cys Cys Ser Pro Ser Ser Arg
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Thr Ser Ser Ser Leu Ser Trp Arg Met Gly Ser Gln Ile Arg Pro Ser
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<400> 1360
Met Ala Phe Tyr Leu Trp Cys Phe His Ala Val Phe Phe Thr Val Cys
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                              -10
Val Cys Val Arg
      1
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Met Thr Leu Asn Glu His Ala Ala Phe Lys His Leu Phe Asn Lys Ala
            - 30
                            -25
His Leu Ala Pro Pro Leu Ile His Leu Thr Leu Ser Gly His Ser Thr
         -15
                             -10
                                                - 5
Cys Phe Arg Glu His Arg Val Gly Gly Lys Val Ile Asp Glu Gln His
                                        10
Pro Lys Ala Glu Glu Ser Phe Leu Val Gln Glu Gly
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<210> 1362
<211> 29
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<222> -26..-1
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Met Ser Phe Ser Ser Leu Pro Pro Ser Leu Pro Pro Ser Leu Ala
                        -20
                                           -15
Ser Phe Leu Leu Thr Phe Leu Pro Ser Leu Pro Arg
-10
                    -5
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Met Arg Ala Gln Gly Leu Ser Cys Gly Tyr Pro Ala Arg Pro Leu Gln
 -45
                       -40
Pro Phe Leu Glu His Leu Ala Gly Ser Gly Ile Thr Lys Arg Thr Ala
-30
                   -25
                                        -20
                                                            -15
Pro Gly Cys Ala Pro Leu Arg Trp Val Pro Gln Ile Arg Gly Cys Pro
               -10
Leu Thr Arg Leu Ala Gln Arg Gly Ala Asp Thr Arg Thr Arg Glu Asn
                           10
                                               15
Leu Phe Tyr Ser Arg Phe Pro Gly Leu Gln Leu Pro Ala Ala Xaa Xaa
                       25
Ser Ala Ser Ala Leu Ser Leu Cys Thr Pro Arg Ser Pro Pro Leu Pro
                . 40
                                       45
Leu Pro Leu Pro Ile Asn Ser Pro Gly
               55
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<221> SIGNAL <222> -37. -1

<400> 1364

Met Ala Ala Ser Ser Thr Ser His Leu Lys Asn Lys Thr Lys Thr Phe
-35
-30
-25

Leu Ala Pro Met Thr Asn Cys His Ser Ile Ser Phe Leu Pro Phe Gln
-20 -15 -10

Ala Ser Ile Phe Gly Lys Thr Arg Leu Gln Ser Leu Arg Pro Ser His -5 10

Pro Tyr Pro His

<210> 1365

<211> 43

<212> PRT

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<222> -39..-1

<400> 1365

Met Pro Lys Asp Ala Asp Leu Ala Phe Ser Ala Ser Leu Phe Glu Arg
-35 -30 -25

Ala Glu Ser Leu Tyr Thr Leu Ile Ser Lys Phe Xaa Ser Cys Xaa Cys
-20 -15 -10

Val Ser Thr Leu Ala Tyr Thr Lys Gly Arg Gly

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<211> 30

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<222> -28..-1

<400> 1366

Met Phe Val Asn Arg Thr Cys Phe Asn Ser Ser Phe Pro Ile Trp Met
-25 -20 -15

Pro Phe Leu Phe Leu Thr Leu Phe His Cys Leu Gly Arg Arg -10 -5 1

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<211>. 63

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<222> -37..-1

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Met Xaa Gly Ser Ser Arg Xaa Xaa Gly Leu Gln Ile Thr Ala Ser Arg
-35 -30 -25

Thr Gly Lys Val Tyr Pro Ala Cys His Phe Leu Xaa Ala Val Ser Ala
-20 -15 -10

Ser Ser Ser Xaa Ala Cys Leu Trp Tyr Arg Pro Ile Ala Arg Arg Pro
-5 1 5 10

Ala Gly Pro Gly Gly Ser Leu Ser Ser Ala Gln Val His Pro Ala 15 20 25

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                         -20
 Trp Leu Leu Cys Arg Ile Cys Thr Phe Gly Phe His Gly Phe Ser Lys
                    - 5
 Tyr Thr Val Ser Arg Gly Thr Gln Gln Gly Ala Gly Xaa Xaa Xaa Gly
                                 15
 Leu His Gln Asn Trp Glu Gln Trp Arg Gly Leu Val Gly Lys Ser Ser
                             30
 Ser Ala Ala Val Val Phe Cys Leu Thr Phe Asp Leu Val Thr Ser Phe
                        45
                                            50
 Gln Leu Ala Ser Ala Ile Glu Ser Thr His Phe His Ala Gly Arg Asp
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 Gly Ser His Leu
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 Met Glu Leu Ser Leu Pro Pro Ser Met Cys Asp Tyr Pro Xaa Phe Cys
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                                   -20
Leu Leu Phe Pro Ala Ser Leu Arg Leu Cys Val His Pro
                                - 5
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 <211> 27.
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Met Asp Gln Lys Pro Leu Phe Thr Val Gly Cys Ala Gly Leu Ala Gly
                   -15
Ser Cys Arg Gly Ile Ser Phe Leu Arg Thr Arg
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<211> 45
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -23..-1
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 Met Ser Val Asn Xaa Ile Phe Ile Phe Tyr Phe Ile Leu Leu Leu
             -20
                                 -15
 Ile Gln Asp Leu Thr Met Ser Pro Thr Ala Gly Met Gln Trp His Asn
      - 5
                             1
 His Gly Pro Pro Gln Ala Leu Pro Cys Pro Leu Arg Xaa
                     15
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 <211> 78
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
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 <400> 1372
 Met Ser Phe Leu Asn Val Asp Ile Thr Asp Cys Leu Tyr Asn Pro Ser ,
                  -40
                                        -35
 Val Cys Pro Val Ala Gln Ser Ser Leu Thr Cys Asp Phe Ile Asp Gly
                 -25
                                    -20
 Ile Cys Leu Gly Ser Pro Leu Ala Glu Cys Leu Leu Gly Xaa Xaa Xaa
             -10
                                - 5
 Xaa Ile Xaa Gly Ile Asn Xaa Xaa Cys Phe Pro Cys Gly Val Lys Cys
                       10
                                            15
 Ala Gly Val Val Leu Gly Leu Ser Thr Leu Trp Tyr Val Val
                    25
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Met Lys Val Gly Lys Asp Ser Leu Glu Ser Leu Pro Ser Leu Cys Glu
                            -30
Lys His Ile Gly Pro Ser Gly Leu Phe Thr Phe Leu Ser Pro Ser Phe
                        -15
                                            -10
His Ser Val His Leu Ser Glu Leu Asn Glu Leu Tyr Thr Ile Ala Ala
- - 5
Gly
<210> 1374
<211> 30
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -17..-1
<400> 1374
Met Glu Ser Lys Val Leu Ile Ser Ala Ser Leu Leu Arg Ala Ser Gln
       -15
                           -10
Leu Lys Ile Lys Xaa Asn Lys Met Thr Asn Phe Leu Ile Leu
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<213> Homo sapiens
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Met Ala Ala Ser Val Leu Asn Thr Val Leu Arg Arg Leu Pro Met Leu
               -20
                                    -15
Ser Leu Phe Arg Gly Ser His Xaa Xaa Phe Arg Phe Pro Ser Arg Leu
            - 5
Phe Ala Pro Lys Leu Pro Leu Arg Lys Ile Leu Cys Pro Gln Phe Pro
                        15
Phe Leu Leu Ile Arg Met Ser Pro Gly Asn Ile Trp Asn Gln Lys Asn
                   30
                                        35
Thr Arg Ser Asp Met Val Leu Ala Pro Ser Gly Leu Thr Thr Ala Ala
                45
Thr Thr Arg Val Val Tyr Pro His Ser Gly Leu Gly Arg His Val Phe
                                б5
Val Gly Ile Lys Leu Leu Gly Ile Pro Ala Pro Ser Val Glu Ile Thr
                          80
       75
Ser Cys Met Leu Thr Leu
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Met Lys Ser Asn Leu Thr Leu Leu Thr Cys Leu Xaa Leu Xaa Gly Gly
                                -10
            -15
Glu Gly Trp Lys Gly Ala Ala Val Cys Phe Glu Thr Val Glu Gln Phe
Cys Ser Leu Arg Lys Trp His Val Thr Tyr Leu Xaa Lys Asp Ser Gly
                   20
Leu Cys Gln Gln Gln Glu Lys Leu Tyr Thr Lys Phe Leu Val Cys Ile
               35
Lys Gly Ala Ser Asn Glu Glu Ile Lys Lys Thr Tyr
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 Met Asn Ile Ile Leu Glu Ile Leu Leu Leu Ile Thr Ile Ile Tyr
                 -15
                                     -10
 Ser Tyr Leu Glu Ser Leu Val Lys Phe Phe Ile Pro Gln Arg Arg Lys
            1
 Ser Val Ala Gly Glu Ile Val Leu Ile Thr Gly Ala Gly His
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Met Asp Leu Ile Gly Phe Gly Tyr Ala Ala Leu Val Thr Phe Gly Ser
                -35
                                     -30
Ile Phe Gly Tyr Lys Xaa Arg Gly Gly Val Pro Ser Leu Ile Ala Gly
             -20
                                -15
Leu Phe Val Gly Cys Leu Ala Gly Tyr Xaa Ala Tyr Arg Val Ser Asn
        - 5
                             1
Asp Lys Arg Asp Val
10
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Met Glu Gly Val Ala Xaa Xaa Thr Phe Leu Ala Ala Xaa Arg Arg Leu
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                                    -10
Val Thr Gly Gln Thr Ser Pro Arg Gly Thr Trp Cys Leu Tyr Pro Gly
Phe Cys Arg Ser Val Ala Cys Ala Met Pro Cys Cys Ser His Arg Ser
                        20
                                            25
Cys Arg Glu Asp Pro Gly Thr Ser Glu Ser Arg Glu Met Val Arg Val
30
                    35
Arg Asp His Gly
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<210> 1385 <211> 61 <212> PRT <213> Homo sapiens

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-55
                    -50
                                   -45
Lys Pro Glu Leu Tyr Glu Val Arg Gln His Gly Arg Ala Val Cys Gly
                -35
                                    -30
Gly Glu Asp Asn Ala Ser Pro Gly Glu Gly Leu His Gln Gly Leu Cys
            -20
                                -15
Leu Pro Gln Arg Val His Cys Ser Leu Leu Pro Ala Pro
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Met Pro His Ser Phe Val Ser Cys Asn Leu Phe Leu Ser Val Leu Asn
      -20
                           -15
Phe Leu Phe Leu Leu Ser Phe Ser Thr
  -5
                        1
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Met Ala Val Phe Leu Gln Lys Arg Lys His Thr Met Arg His His Leu
                        -20
                                           -15
Leu Leu Ser Thr Leu Ala Thr Ile Ala Gly Asn Ile Tyr Arg
-10
                   - 5
<210> 1388
<211> 47
<212> PRT
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<222> -26..-1
<400> 1388
Met Ala Asp Ser Glu Ala Leu Pro Ser Leu Ala Gly Asp Pro Val Ala
                       -20
                                           -15
Val Glu Ala Leu Leu Arg Ala Val Phe Gly Val Val Val Asp Glu Ala
                   - 5
                                        1
Ile Gln Lys Gly Thr Ser Val Ser Gln Lys Val Cys Xaa Trp Lys
           10
                               15
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<212> PRT

<220>

<213> Homo sapiens

<221> SIGNAL

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-10
-5

Gln Arg

<210> 1393

<211> 53

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<213> Homo sapiens

<220>

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<222> -25..-1

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Met His Lys Phe Phe Arg His Phe Tyr Ser Asp Phe Leu Ile Tyr Phe -25 -15 -10

Phe Gln Leu His Ser Cys Cys His Asp Lys Val Thr Ala Xaa Arg Ala

Tyr Xaa His Tyr Ser Ser Leu Leu Thr Pro Tyr Leu Ser Gln His Pro
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Cys Pro His Pro Gly 25

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<222> -26..-1

<400> 1394

Met Ala Ala Leu Gly Ser Pro Ser His Thr Phe Arg Gly Leu Leu Arg
-25
-15

Glu Leu Arg Tyr Leu Ser Ala Ala Thr Gly His Pro Ile Ala Thr Pro -10 -5 1 5

Arg Pro Ile Gly Thr Xaa Val Lys Ala Phe Arg Ala His Arg Val Thr

Ser Glu Lys Leu Cys Arg Ala Gln His Glu Leu His Phe Gln Ala Ala 25 30 35

Thr Tyr Leu Cys Leu Leu Arg Xaa Ser Gly Asn Met Trp Pro Tyr Ile 40 50

Arg Asn Phe Met Ala Arg Val Ser Ala Arg Trp Arg Ser Leu Leu Ala 55 65 70

Trp Trp Val Ser Ser Cys Pro Ile Ser Leu Glu Gly Arg Ala Gly Ser 75 80 85

His Glu His Gly Glu Tyr Pro Trp Met
90 95

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                                   -20
   Ser Leu Phe Leu Leu Val Val Leu Tyr His Tyr Ala Ala Val
                                                      -15
          -10
                               -5
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  Leu Asn Ile Ser Leu Ile Ser Arg Lys
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  -15
                      -10
                                            ~ 5
 Arg Asn Ser Ser Leu Ala Met
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 <222> '-15..-1
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 Met Glu Ser Cys Thr Val Gly Cys Ala Thr Ala Ser Ser Trp Gly Cys
 -15
                   -10 .
 Thr Ser Arg
 <210> 1399
 <211> 71
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 <213> Homo sapiens
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 <222> -43..-1
<400> 1399
Met Ala Met Ser Phe Glu Trp Pro Trp Gln Tyr Arg Phe Pro Pro Phe
                                -35
                                                   -30
Phe Thr Leu Gln Pro Asn Val Asp Thr Arg Gln Lys Gln Leu Ala Ala
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-25
                              -20
   Trp Cys Ser Leu Val Leu Ser Phe Cys Arg Leu His Lys Gln Ser Ser
      -10 .
                          - 5
                                             1
   Met Thr Val Met Glu Ala Gln Glu Ser Pro Leu Phe Asn Asn Val Lys
                  10
                                  · 15
   Leu Gln Arg Lys Leu Pro Val
               25
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                  -10
                                - 5
  Pro Phe Leu Ser Pro Pro Leu
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 Met Leu His Phe Xaa Tyr Met Ile Xaa Val Cys Leu Glu Arg Met Cys
                  -20
                                            -15
 Ile Leu Gln Leu Leu Ser Ala Val Leu Tyr Arg Phe
                     - 5
 <210> 1402
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 <222> -30..-1
 <400> 1402
Met Ser Ser Glu Pro Pro Pro Pro Pro Pro Pro Pro Pro Thr His Gln Ala
                   -25 - -20
Ser Val Gly Leu Leu Asp Thr Pro Leu Gly Ala Val Ser Ala His His
                -10
                                   -5
 Pro Leu Cys
   . 5
<210> 1403
<211> 29
<212> PRT
<213> Homo sapiens
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<222> -20..-1
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  Met Phe Leu Asp His Val Arg Phe Leu Thr Ser Ile Ser Phe Leu Ala
 -20
          -15
                           -10
  Leu Val Leu Trp Asn Val Phe Leu Asn Ser Thr Arg Leu
  <210> 1404
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 <222> -19..-1
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             -15
                                -10
 Ala Leu Ala Ser Gln Ile His Cys Arg Val
            1
                           5
 <210> 1405
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 <222> -26..-1
 <400> 1405
Met Pro His Asn His Leu Glu Gly Asp Ala Leu Leu Arg Val Pro Val
  -25 -20
                                         -15
Leu Cys Ile Trp Arg Ala Trp Leu Arg Ala Glu Val Gly Gly Arg Ala
                  - 5
                                     1
Pro Leu Pro Gly Arg Met
           10
<210> 1406
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Met Lys Asn Thr Leu Tyr Tyr Asn Phe Cys Leu Phe Trp Ile Xaa Leu
    -20
                         -15
Pro Pro His Thr Cys Thr His Thr Asp Thr His
  -5
                      1
<210> 1407
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WO 99/53051 612 <400> 1407 Met Cys Leu Asn Pro Ala Cys Ser Gly Pro Leu Ser Leu Arg Ser Pro -30 -25 Arg Leu Pro Pro Leu Phe Cys Thr Phe Leu Ser Leu His Pro -15 -10 Trp Gly Gly Phe Phe Leu Cys Ala Trp Ile Ser Xaa Phe Leu Pro Trp 5 Val Cys Val Xaa Ala 15 <210> 1408 <211> 101 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -89..-1 <400> 1408 Met Ala His Ser Lys Thr Arg Thr Asn Asp Gly Lys Ile Thr Tyr Pro -80 Pro Gly Val Lys Glu Ile Ser Asp Lys Ile Ser Lys Glu Glu Met Val -65 Arg Arg Leu Lys Met Val Val Lys Thr Phe Met Asp Met Asp Gln Asp -50 Ser Glu Glu Lys Glu Leu Tyr Leu Asn Leu Ala Leu His Leu Ala -45 -35 Ser Asp Phe Phe Leu Lys His Pro Asp Lys Asp Val Arg Leu Leu Val -20 -15 Ala Cys Cys Leu Ala Asp Ile Phe Arg Ile Tyr Ala Pro Glu Ala Pro Tyr Thr Ser Pro Lys 10 <210> 1409 <211> 26 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1 <400> 1409 Met Xaa Ser Cys Glu Ile Ala Trp Thr Ala Thr Pro Ser Ser Ala Ala -15 -10 Phe Ala Gln Ala Phe Pro Thr Ala Cys Asn 1 5 <210> 1410 <211> 46 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -25..-1

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Ala Ser Arg Ala Gly Asn Leu Gly Val Trp Thr Glu Lys Gly
                              15
  <210> 1411
  <211> 29
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  <222> -27..-1
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 Met Xaa Ser His Arg Leu Phe Gly Cys Phe Pro Ser Asp Leu Ser Arg
         -25
                              -20
 Met Val Leu Leu Ser Ser Ala Leu Leu Ser Thr Glu Asn
                         - 5
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 Met Arg Pro Ser His Ser Ser Ala Tyr Leu Cys Leu His Leu Cys Ala
   -20
                         -15
 Phe Ser Thr Glu Gly Trp Met Asn Arg Leu Ser Ser Leu Arg Leu
Ala Pro Leu Pro Leu Tyr Pro Phe Cys Leu Pro Ser Asn Ser Pro
            15
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<400> 1413
Met Trp Ser Arg Leu Val Trp Leu Gly Leu Arg Ala Pro Leu Gly Gly
    -15
                        -10
Arg Gln Gly Phe Thr Ser Lys Ala Asp Pro Gln Gly Ser Gly Arg Ile
                                    10
Thr Ala Ala Val Ile Glu His Leu Glu Arg Leu Ala Leu Val Asp Phe
           20
                                25
Gly Ser Arg Glu Ala Val Ala Arg Leu Glu Lys Ala Ile Ala Phe Ala
Asp Arg Leu Arg Ala Val Asp Thr Asp Gly Val Glu Pro Met Glu Ser
                        55
Val Leu Glu Asp Arg Cys Leu Tyr Leu Arg Ser Asp Asn Val Val Glu
                   70
Gly Asn Cys Ala Asp Glu Leu Leu Gln Asn Ser His Arg Val Val Glu
Glu Tyr Phe Val Ala Pro Pro Gly Asn Ile Ser
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  Leu Glu Glu Gly Ser Pro Gly Ser Gly Thr Tyr Thr Arg His Gly Tyr
                   -60
                                         -55
  Ile Phe Ser Ser Leu Xaa Gly Cys Leu Met Lys Ser Ser Glu Asn Gly
                  -45
                                     ~40
  Ala Leu Pro Val Val Ser Val Val Arg Glu Thr Glu Ser Gln Leu Leu
             -30
                                 - 25
  Pro Asp Val Gly Ala Ile Val Thr Cys Lys Ser Leu Ala Ser Ile His
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         -15
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  Ala Leu Pro
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 Met Val Gly Asn Gln Gly Pro Gln Pro Pro Pro Phe Pro Met Glu Pro
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                                        -50
 Thr Met Ala Gln Tyr Gln Ala Ile Ser Lys His Leu Pro Lys Val Cys
                -40
                                     -35
                                                        -30
 Gln Glu Pro His Leu Pro Arg Gly His Leu Gln Pro Gln Gln His Arg
            -25
                                 -20
                                                    -15
 Leu Leu Val Ala Arg Leu His Met Ala Ser Leu Ala Arg Arg Cys Thr
                            - 5
 Glu Trp Ala Lys Leu His Cys Ser Asp Ala Arg Leu Pro Trp Val Ser
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Met Lys Pro Gln Thr Leu Ala Val Ser Val Thr Val Leu Lys Asp Gly
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Val Ala Gly Val Cys Phe Phe Arg Arg Ser Asp Ala Ser Glu Val Ser
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Ser Phe Trp
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615
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Met Val Val Leu Ile Cys Leu Ser Leu Met Ile Ser Asn Thr Glu Leu
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 Phe Phe Ile Arg Phe Leu Thr Ala Cys Met Pro Ser Phe Glu Lys Cys
     -25
                            -20
                                               -15
Leu Phe Leu Ser Phe Ala His Phe Leu Met Gly Arg Thr His Arg
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Met Ser Ser Leu Tyr Ile Leu Asp Ile Ser Leu Leu Ser Asp Ile Leu
        -20
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Phe Ala Asn Ile Phe Ser His Ser Trp Asp Val Phe Pro Leu Ser Phe
 - 5
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Leu Phe Phe Ser
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Met Gly Gln Gly Ala Arg Gly Trp His Arg Glu Pro Gly Leu Gly Leu
               -80
                                   -75
Arg His Ser Pro Arg Arg Leu Ser Gly Ala Leu His Leu Glu Ala Gly
           -65
                               -60
Cys Asp Arg Asn Ala Thr Thr Val Arg Pro Leu Arg Ala Lys Xaa Gly
                           -45
Asp Ala Leu Pro Glu Glu Ile Arg Glu Pro Ala Leu Arg Asp Ala Gln
                       -30 .
                                           -25
Trp Val Arg Asp Gln Leu Ala Ser Ser Leu Leu Ile Ile Leu Leu Pro
                  -15
                                    -10
Asn Thr Gln Asp Leu Arg Ile Gln Lys Asp Pro Thr Pro Gly Pro
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   Cys Lys Asn Phe Leu Lys Lys Trp Arg Met Lys Arg Glu Ser Leu Met
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   Glu Trp Leu Asn Ser Leu Leu Leu Leu Cys Leu Tyr Ile Tyr Pro
                                                    -20
                           -10
   His Ser His Gln Val Asn Xaa Xaa Ser Ser Leu Leu Thr Met Asp Leu
                                               -5
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   Gly Arg Val Asp Xaa Xaa Asn Glu Ser Arg Phe Ser Val Val Tyr Thr
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   Pro Val Thr Asn Thr Thr Pro
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  Met Cys Thr Cys Leu Cys Val Cys Leu Tyr Met Tyr Asn Met Gln Phe
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 Leu Xaa Phe Val Phe Val Cys Xaa Leu Leu Lys Cys Met Ser Val Pro
 Leu
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 Met Ala Ala Ser Ala Ala Ala Glu Leu Gln Ala Ser Gly Gly Pro
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                        -25
 Arg His Pro Val Cys Leu Leu Val Leu Gly Met Ala Gly Ser Gly Lys
 -15
                     -10
 Thr Thr Phe Val Gln Arg Leu Thr Gly His Leu His Ala Gln Gly Thr
                                 10
Pro Pro Tyr Val Ile Asn Leu Asp Pro Ala Val His Glu Val Pro Xaa
Pro Ala Asn Ile Asp Ile Arg Asp Thr Val Lys Tyr Lys Glu Val Met
Lys Gln Tyr Gly Leu Gly Pro Asn Gly Gly Ile Val Thr Ser Leu Asn
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Leu Phe Xaa Thr Arg Phe Asp Gln Val Met Lys Leu Leu Arg Arg Pro
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Arg Thr Cys Pro Asn Met Cys
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WO 99/53051
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  Met Tyr Ala Cys Ala Met Leu Val Leu Leu Thr His Gly Leu Ile His
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  Tyr Ser Phe Thr His His Leu His Tyr Val Phe Ile Leu Ile Leu Pro
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  Leu Pro Pro Pro Gln
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 Met Gly Phe Leu Gly Ser Pro Arg Gln Arg Asn Ser Met Cys Leu Leu
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                                    -15
 Leu Asp Val Ser Ser Xaa Lys Ser Thr Asp Asn Xaa Xaa Xaa Xaa
                                                         -10
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 Leu Ile Ile Tyr Tyr Leu Ile Thr Arg Lys Gly Pro Gly
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Met Ser Cys Gln Xaa Xaa Leu Ala Xaa Thr Leu Thr Trp Leu Met Ile
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Arg Gly Arg His Pro Tyr Leu Thr Arg Arg Ser Ala Arg Asn Phe Asn
                            -20
                                                -15
Ile Phe Leu Ala Ala Pro Ser Pro Val Trp Gln Pro Gln Arg Thr Arg
   -10
                      - 5
Arg Pro Gln
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Met Cys Pro Ala Trp Leu Pro Cys Trp Thr Ala Gln Thr Glu His Leu
               -30
                                  -25
Asp Arg Tyr Arg Lys Phe His Gln Met Ala Leu Xaa Pro Gly Thr Ser
           -15
                               -10
Arg Ala Gln Ala Leu Leu Tyr Asn Glu Val Leu Glu Arg Phe Met Phe
                       5
Thr Arg Leu
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618
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  Met Asn Val Met Lys Arg Ile Cys Thr Phe Leu Leu Pro Ser His Ser
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  Thr Ser Gly Pro Leu Cys Cys Ser Asn Ala His Leu Pro Ala Thr Ser
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  Ser Thr Leu Lys His Cys Arg Ala Trp Arg Glu Ala
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 Met Val Val Phe Gly Tyr Glu Ala Gly Thr Lys Pro Arg Asp Ser Gly
     -120
                         -115
                                              -110
 Val Val Pro Val Gly Thr Glu Glu Ala Pro Lys Val Phe Lys Met Ala
                     -100
                                          -95
 Ala Ser Met His Gly Gln Pro Ser Pro Ser Leu Glu Asp Ala Lys Leu
                 -85
                                     -80
 Arg Arg Pro Met Val Ile Glu Ile Glu Lys Asn Phe Asp Tyr Leu
                                                         -75
             -70
                                 -65
                                                      -60
 Arg Lys Glu Met Thr Gln Asn Ile Tyr Gln Met Ala Thr Phe Gly Thr
         -55
                             -50
 Thr Ala Gly Phe Ser Gly Ile Phe Ser Asn Phe Leu Phe Arg Arg Cys
                         -35
                                             -30
 Phe Lys Val Lys His Asp Ala Leu Lys Thr Tyr Ala Ser Leu Ala Thr
 -25
                     -20
                                         -15
 Leu Pro Phe Leu Ser Thr Val Val Thr Asp Lys Leu Phe Val Ile Asp
                 -5
 Ala Leu Tyr Ser Asp Asn Ile Ser Lys Glu Asn Cys Val Phe Arg Ser
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                            15
Ser Leu Ile Gly Ile Val Cys Gly Val Phe Tyr Pro Ser Ser Xaa Ala
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Phe Thr
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-35
                                -30
  Val Ala Gly Leu Ile Gly Ala Ser Val Leu Val Val Cys Val Ser Val
                                                   -25
  -20
                            -15
                                            -10
  Thr Val Phe Val Trp Ser Cys Cys Xaa Gln Gln Ala Glu Lys Lys His
                     1
                                     5
  Lys Asn Pro Pro Tyr Lys Phe Ile His Met Leu Lys Gly Xaa Ser
                 15
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 Met Val Ile Leu Thr Met Leu Ile Leu Leu Ile His Glu His Gly Ile
  -15
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                                      -5
 Phe Phe Ser Leu Val Cys Val Leu Phe
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 <222> -29..-1
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 Met Phe Ser His Asn His Ser Tyr Thr Tyr Thr Pro Gln His Ser Pro
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                    -20
 Leu Thr His Thr His Thr Cys Thr Pro Pro Ser Thr Ala His Pro Arg
                                                     -15
            -10
                             -5
 Gly
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Met Phe Xaa Met Ile Leu Leu Cys Phe Leu Ala Val Ser Asn Phe Asn
-15 -10
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Lys Leu Leu Trp Gly Xaa
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  Met Phe Leu Ile Leu Gly Lys Phe Ser Arg Val Met Gly Leu Pro Leu
                          -20
                                              -15
  Ala Cys Phe Ser Leu Phe Gly Xaa Leu Pro Gln Gly Leu Leu Ile
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  <222> -19..-1
 <400> 1434
 Met Val Ala Leu Gly Gln Leu Ala Xaa Leu Pro Gly Xaa Xaa His Gly
             -15
                             -10
 Gly Leu Ser Ala Val Thr Val Val Leu Pro Ile Leu Leu Cys
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 Met Pro Val Ser Phe Val Cys Leu Leu Phe Arg Asn Val Tyr Ser Asn
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                                        - 5
 Leu Leu Pro Ser Phe Phe
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 <222> -27..-1
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Met Gly Ser Gly Gly Asp Ser Leu Leu Gly Gly Arg Gly Ser Leu Pro
                            -20
                                                -15
Leu Leu Pro Ala His His Gly Arg His Gly Ser Gly Leu Pro Ala
                        -5
Pro Asp Pro Ser Pro Pro Pro Gly Pro Ala Val Pro Gly Pro Trp Pro
                10
                                   15
                                                       20
Cys Gln Asp Glu Leu Pro Ser Leu Arg Pro Ala Thr Ser His His Phe
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 Met Ala Val Gly Gly Thr Ala Val Ile Thr Arg Arg Leu Leu Gly Arg
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                                          -15
 Ser Gly Phe Ser Phe Gln Val Ser Gly Trp Gly Trp Gly Glu Arg Val
                  - 5
 Asp Asp Phe Leu Phe Ser Ser Gly Ile Asp Gly
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 Met Arg His His Val Arg Xaa Pro Ala Leu Ser Ser Leu Ala His His
                         -15
 Pro Arg Thr Ser Gly Gln Lys Arg Glu Pro Ile Ala Pro Ala Gln Leu
 - 5
                                     5
 Ser Pro
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Met Leu Ile Leu Asn Gly Phe Arg Gly His Ala Thr Asp Ser Val Lys
            -70
                                 -65
                                                     -60
Asn Ser Met Glu Ser Met Asn Thr Asp Met Val Ile Ile Pro Gly Gly
        -55
                             -50
Leu Thr Ser Gln Leu Gln Val Leu Asp Val Val Val Tyr Lys Pro Leu
                         -35
Asn Asp Ser Val Arg Ala Gln Tyr Ser Asn Trp Leu Leu Ala Gly Asn
                    -20
                                         -15
Leu Ala Leu Ser Pro Thr Gly Asn Ala Lys Lys Pro Pro Leu Gly Leu
                -5
                                     1
Phe Leu Glu Trp Val Met Val Ala Trp Asn Ser Ile Ser Ser Glu Ser
        10
                            15
Ile Val Gln Gly Xaa Lys Glu Val Pro Tyr Leu Xaa Gln Leu Gly Gly
   25
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Gly Arg Arg
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<222> -25..-1
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Met Ile Cys Thr Thr Val Tyr Ile Thr Met Ala Pro Tyr Cys Leu Ser
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WO 99/53051
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                                       622
  -25
                      -20
                                          -15
  Asn Cys Leu Leu Xaa Xaa Ser Trp Gly Leu His Leu Tyr Arg Phe Leu
                 - 5
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  Ala Pro
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Met Leu Ser Ile Phe Ser Phe Phe Cys Arg Pro Phe Val Tyr Leu Leu
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                                    -15
Leu Arg Asn Leu Xaa Ser Tyr Ser Leu Pro Thr Thr
<210> 1443
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Met Phe Pro Val Ser Ser Gly Cys Phe Gln Glu Gln Glu Thr Asn
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Lys Ser Leu Pro Arg Ser Ala Ser Thr Pro Glu Thr Arg Thr Lys Phe
                        -55
                                             -50
Thr Gln Asp Asn Leu Cys Xaa Ala Gln Arg Glu Arg Leu Asp Ser Ala
                    -40
                                        -35
Asn Leu Trp Val Leu Val Asp Cys Ile Leu Arg Asp Thr Ser Glu Asp
                -25
                                    -20
                                                         -15
Leu Gly Leu Gln Cys Asp Ala Val Asn Leu Ala Phe Gly Arg Arg Cys
                               - 5
Glu Glu Leu Glu Asp Ala Arg His Lys Leu Gln Xaa His Leu
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WO 99/53051 623 <222> -15..-1 <400> 1444 Met Pro Leu Val His Ser Phe Leu Trp Leu Ser Ser Ile Leu Tyr Ile -10 Tyr His Leu Arg <210> 1445 <211> 56 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -24..-1 <400> 1445 Met Ile Ser Asn Gly Lys Phe Phe Cys Phe Phe Xaa Val Phe Xaa Phe -20 -15 Xaa Phe Leu Xaa Arg Xaa Leu Xaa Xaa Yaa Pro Arg Leu Glu Cys Asn - 5 1 Gly Lys Xaa Ser Ala His Xaa Asn Leu Arg Leu Leu Ser Xaa Ser Asn 10 15 Ser Leu Ala Ser Ala Pro Arg Gly 30 <210> 1446 <211> 101 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -90..-1 <400> 1446 Met Glu Asp Ser Ala Ser Ala Ser Leu Ser Ser Ala Ala Ala Thr Gly -85 -80 Thr Ser Thr Ser Thr Pro Ala Ala Pro Thr Ala Arg Lys Gln Leu Asp -70 -65 Lys Glu Gln Val Arg Lys Ala Val Asp Ala Leu Leu Thr His Cys Lys -55 -50 -45 Ser Arg Lys Asn Asn Tyr Gly Leu Leu Leu Asn Glu Asn Glu Ser Leu -40 -35 Phe Leu Met Val Val Leu Trp Lys Ile Pro Ser Lys Glu Leu Arg Val -20 -15 Arg Leu Thr Leu Pro His Ser Ile Arg Ser Asp Ser Glu Asp Ile Cys -10 Xaa Phe Thr Lys Asp . 10 <210> 1447 <211> 59 <212> PRT

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<400> 1447

Met Asn Ala Glu Gly Ala Ser Pro Gly Lys Glu Thr Asn Thr Gly Thr

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624
                  -25
                                      -20
                                                          -15
  Leu Ile Glu Leu Asn Leu Xaa Ser Pro Val Ala Leu Gln Trp Pro Leu
              -10
                                  -5
  Ser Ser Pro Ser Cys Leu Arg Ile Leu Ser Asn Lys Val Pro Arg Asn
                         10
  Leu Arg Trp Gln Lys His Tyr Ser Thr His Gln
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 Met Leu Gly Leu Asp Glu Leu Gly Arg Ser Gly Cys Gly His Cys Thr
 Gln Ala Asp Leu Arg Phe Gly Asp Ala Ala Gly Xaa Glu Pro Arg Xaa'
                             -40
                                                  -35
 Arg Xaa Thr His Arg Asn Thr Ala Ala Ala Arg Val Pro Pro Pro Pro
     -30
                         -25
                                             -20
 Arg Val Met Ala Ala Ala Ala Leu Arg Ala Pro Ala Gln Ser Ser
 -15
                     -10
                                         - 5
 Val Thr Phe Glu Asp Val Ala Val Asn Phe Ser Leu Glu Glu Trp Ser
                                 10
 Leu
 <210> 1449
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Met Ser Ala Leu Lys Asp Phe Arg Glu Phe Leu Asn Trp Trp Gly Asn
 -25
                        -20
                                            -15
Leu Ser Phe His Leu Gln Glu Ala His Gly Ser Glu Ile Ala Glu Met
-10
                    -5
                                        1
Gly Ala Gly Ile Leu Glu Glu Lys Asn Tyr Gly Gln Gln Xaa His Cys
Asn
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Met Ser Leu Pro Pro Phe Phe His Pro Ser Pro Ala Pro Ser Leu Ala
                  -25
                                       -20
Pro Pro Pro Ser Leu Phe Leu Ser Leu Pro Pro Ser Leu Ser Pro Pro
                                    - 5
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Leu Pro Ala Arg

<222> -25..-1

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 <400> 1451
Met Phe Phe Leu Cys Gly Phe Leu Tyr Leu Cys Phe Ile Ser Phe Phe
 Phe Phe
   5
 <210> 1452
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Met Lys Ala Gly Pro Cys Ser Cys Gln Glu Gly Gly Arg Gln Trp Ala
                           -35
                                     . -30
His Gly Ser Val Pro Leu Gln Pro Thr Ala Arg Leu Ala Ala Leu Gly
 -25
                       -20
                                          -15
Ile Phe Leu Cys Pro Gly Glu Thr Leu Ser Ala Ser Leu His Trp Asn
-10
                   -5
                                       1
Pro Ile Gly
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Met Leu Ser Gln Ser Phe Gln Lys Asn Lys Thr Asn Leu Leu Cys Leu
           -20
                              -15
Thr Phe Gln Arg Cys Gln Ser Tyr Asn Trp Leu Asn Ile Phe Glu Ala
 -5
Thr Tyr Met Thr Thr Leu Phe Ile Ser Val Ile Xaa Thr Asn Phe Leu
Lys Arg Tyr Leu Leu
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  Met Phe Leu Phe Cys Trp Glu Lys Ser Pro Arg Met Gln Leu Leu Gly
                      -20
                                          -15
  Cys Met Val Leu Tyr Asp Cys Phe Ser Phe Lys Lys Leu Pro Gly
                  - 5
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 <222> -30..-1
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 Met Ser Phe Ile Ser Val Ile Phe Pro Leu Ile Leu Leu Asn Arg Phe
                     -25
                                         -20
 Ser Phe Val Cys Phe Phe His Val Phe Tyr Cys Val Phe Cys Asn Val
                 -10
                                     - 5.
 Ser Ser Leu Phe Ser Tyr Gln Phe Leu Leu His Phe Cys Asp Asp
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 <222> -31..-1
 <400> 1456
Met His Glu Tyr Leu Pro Arg Asn Phe His Asp Phe Asn Ser Pro Asn
                     -25
                                             -20
Ser Lys Leu Gly Met Gly Met Gly Phe Phe Ser Gly Val Lys Ser Trp
                    -10
                                         - 5
Ile Gly Gly
<210> 1457
<211> 83
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Met Ala Ser Xaa Val Pro Val Lys Asp Lys Lys Leu Leu Glu Val Lys
                        -30
                                            -25
Leu Gly Glu Leu Pro Ser Trp Ile Leu Met Arg Asp Phe Ser Pro Ser
                    -15
                                        -10
Gly Ile Phe Gly Ala Phe Gln Arg Gly Tyr Tyr Arg Tyr Tyr Asn Lys
Tyr Ile Asn Val Lys Lys Gly Ser Ile Ser Gly Ile Thr Met Val Leu
       15
                            20
Ala Cys Tyr Val Leu Phe Ser Tyr Ser Phe Ser Tyr Lys His Leu Lys
   30
                        35
                                            40
His Glu Ser
45
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 Met Val Ile Ser Ala Gly Ala Leu Leu Trp Met Ala Trp Asp Gly Gln
             -15
                                 -10
 Leu Ser Arg Pro Glu Gly Ala Arg
 <210> 1459
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 <222> -18..-1
 <400> 1459
Met Val His Cys Asn Leu Glu Leu Leu Gly Ser Ser Tyr Asn Pro Ile
         -15
                        -10
                                                     -5
Ser Ala Ser Pro Val Ala Arg Thr Ile Ser Cys Pro Ala Ile Val
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Met Leu Gly Ser Gly Phe Lys Ala Glu Arg Leu Arg Val Asn Leu Arg
            -85
                                -80
                                                    -75
Leu Val Ile Asn Arg Leu Lys Leu Leu Glu Lys Lys Lys Thr Glu Leu
        -70
                            .-65
                                                -60
Ala Gln Lys Ala Arg Lys Glu Ile Ala Asp Tyr Leu Ala Ala Gly Lys
                        -50
                                            -45
Asp Glu Arg Ala Arg Ile Arg Val Glu His Ile Ile Arg Glu Asp Tyr
-40
                    -35
                                        -30
Leu Val Glu Ala Met Glu Ile Leu Glu Leu Tyr Cys Asp Leu Leu
                -20
                                   -15
                                                        -10
Ala Arg Phe Gly Leu Ile Gln Ser Met Lys Glu Leu Asp Ser Gly Leu
                               1
Ala Glu Ser Val Ser Thr Leu Ile Trp Ala Ala Pro Arg Leu Gln Ser
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Glu Val Ala Glu Leu Lys Ile Val Ala Asp Gln Leu Cys Pro Ser
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<400> 1461

Met Arg Gly Trp Xaa Ala Pro Ala Trp Arg Xaa Leu Xaa Thr Arg Arg
-40 -35 -30

Leu Pro Met Gly Ser Arg His Gly Ala Ser Pro Ala Ser Ala Val Trp
-25 -20 -15

Cys Leu Xaa Leu Lys Leu Val Pro Ala Leu Cys Ile Ser Gly Leu Thr
-10 -5 1

Leu Gly Ile Gln Gly Phe

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<210> 1462

<211> 49

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<222> -34..-1

<400> 1462

Met Tyr Phe Lys Thr Thr Thr Xaa Xaa His Ser Ala His Met Leu Leu -30 -25 -20

Gln Ile Cys Phe Phe Arg Leu Thr Ile Leu Xaa Phe His Asp Asn Thr
-15 -10 -5

Trp Gly Ser Thr Ser Phe Ser Xaa Val Ala Ala Met Leu Phe His Tyr

1 5 10

Arg

15

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<211> 26

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<400> 1463

Met Ser Ser Asn Ile Gln Arg Leu Gly Phe Pro Leu Leu Phe Leu Phe -20 -15 -10

Phe Leu Phe Phe Phe Phe Phe Phe Phe -5

<210> 1464

<211> 69

<212> PRT

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<222> -67..-1

<400> 1464

Met Cys Asp Ala Phe Val Gly Thr Trp Lys Leu Val Ser Ser Glu Asn
-65 -60 -55

Phe Asp Asp Tyr Met Lys Glu Val Gly Val Gly Phe Ala Thr Arg Lys
-50 -45 -40

Val Ala Gly Met Ala Lys Pro Asn Met Ile Ile Ser Val Asn Gly Asp
-35 -25 -20

Val Ile Thr Ile Pro His Leu Val Leu Pro Leu Pro Met Leu Pro Thr

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WO 99/53051
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 Ser Asn Arg Lys Arg
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 Met Phe Leu Tyr Arg Ser Phe Gly Gly Gln Leu Leu Ser Phe Leu Leu
                        -15
 Gly Thr Tyr Leu Gly Arg Arg Glu Val Ala Gly Pro Gln His Gly Gln
-5
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 Phe Ser Lys
<210> 1466
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<400> 1466
Met Xaa Gly Phe Phe Cys Leu Cys Ala Phe Asn Ser Phe Leu Leu Ser
  -15
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Pro Glu Gly
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Met Ile Phe Pro His Cys Met Tyr Cys Leu Glu Cys Ile Thr Lys Asn
                       -60
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Gly Leu Leu Gly Leu Lys Val Leu Pro Leu Tyr Gly Ile Met Leu Ile
-50
                   -45
                                       -40
Phe Phe Pro Lys Val Val Tyr Asn Asn Gln Pro Leu His Tyr Lys Ser
                     -25
               -30
                                                       -20
Val Met Val Phe Gln Leu Thr Ser Phe Leu Ser Ile Xaa Ile Phe Val
           -15
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Asn Pro Thr Arg
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<213> Homo sapiens

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<210> 1469
<211> 94
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<400> 1469

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Met Ala Ala Ala Thr Leu Thr Ser Lys Leu Tyr Ser Leu Leu Phe Arg
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-25
-20

Arg Thr Ser Thr Phe Ala Leu Thr Ile Xaa Arg Xaa Xaa Ser Cys Ser
-15
-10
-5
Ser Xaa Ala Pro Ser Ile Lys Ala Arg Thr Leu Ser Thr Thr Thr Ser
10
Thr Arg Gly Ser Cys Gly Asn Thr Ser Ser Thr Ser Met Arg Thr Ser
20
25
30

Ser Ser Leu Glu Ala Pro Ile Gln Ala Arg Arg Thr Arg Ser Thr Gln
35 40 45
Gln Leu Phe Ala Gln Ser Trp Ser Leu Ser Xaa Lys Met Met
50 55

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<222> -41..-1

<400> 1470

Met Lys Ala Ile Lys Lys Ser Leu Thr Glu Glu Glu Tyr Leu Tyr Leu
-40 -35 -30

Asp Phe Ser His Gln Thr Glu Gly Cys Ile Phe Pro Leu His Thr Ser
-25 -20 -15 -10

Val Thr Leu Phe Leu Leu Ser Tyr Cys Asp Cys Lys Ile Phe Lys Ile
-5 1 5

Cys Leu Val Val Thr Lys Glu Val Ser Arg Asp Xaa Ser Leu Leu Arg

Asp Asp Leu Ile Gln Asp Val Glu Ile Gln Ile Ile Ser Arg Gln Glu 25 30 35

Leu Pro Pro

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 Met Phe Leu Cys Val Cys Tyr Phe Ile Arg Lys Ser Thr Ser Phe Phe
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 Ser Ile Ser Ser
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 Met Gly Lys Pro Arg Gly Glu Met Leu Glu Val Val Lys Thr Val
 -45
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                                 . -35
                                                            -30
 Ser Thr Phe Thr Leu Gly Gly Trp Lys Gly Thr Ala Pro Val Ser Cys
                 -25
                                    -20
                                                         -15
 Ala Trp Trp Leu Leu Pro Val Trp Lys Leu Gly Gly Gln Leu Glu
             -10
                                -5
Arg Arg Lys Asn Pro Lys Glu Tyr Cys Leu Gly Ser Trp Val Trp Leu
                        10
Ser Pro Gln Leu Ala Pro Arg
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<400> 1473
Met Leu Ile Phe Thr Phe Ile Ser Thr Leu Leu Phe Val Phe Leu Gly
 -15
                        -10
Val Val
1
<210> 1474
<211> 47
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<400> 1474
Met Glu Val Leu Ser Xaa Pro Asn Ser Phe Gln Thr Gln Ala Leu Trp
       -35
                           -30
                                             -25
Asp Ser Leu His Ser Pro Gly Val Pro Gly Ser Gly Leu Cys Ser Met
   -20
                       -15
                                           -10
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Ala Ala Val Gln Ala Gly Asn Gln Ala Ile Tyr Ser Ala Ser Gly

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  <400> 1475
 Met Gln Ala Thr Ala Ser Gln Pro Ile His Phe Phe Xaa Ser Ser Pro
         -40
                              -35
                                                  -30
 Gln Ala Pro Arg His His Ser Gly His Pro Val Pro Leu Leu Thr
                          -20
                                              -15
 Gln Ala Gly Phe Pro Arg Gly Glu Ala Ala Pro Pro Leu Leu
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 Met Arg Gly Xaa Asn Xaa Val Phe Arg Val Phe Ser Glu Ser Leu Lys
 -30
                    -25
                                         -20
                                                             -15
 Gly Leu Cys Thr Phe Thr Leu Asn Leu Thr Ala Val Arg Thr Ile Xaa
                 -10
                                     -5
 Leu Asp
 <210> 1477
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 <222> -32..-1
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Met Gly Arg Ile Ile Pro Met Val Glu Lys Ala Asp Thr Ala Gln Lys
                            -25
                                                 -20
Phe Gln Gly Arg Leu Thr Ile Ser Thr Xaa Leu Ser Thr Ser Xaa Xaa
                        -10
                                            -5
Phe Met Glu Leu Ser Ser Leu Arg
<210> 1478
<211> 112
<212> PRT
<213> Homo sapiens
<220>
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Met Asn Leu Val Ile Cys Val Leu Leu Leu Ser Ile Trp Lys Asn Asn

<222> -67..-1

<400> 1478

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-65
                             -60
 Cys Met Thr Thr Asn Gln Thr Asn Gly Ser Ser Thr Thr Gly Asp Lys
                         -45
                                             -40
 Pro Val Glu Ser Met Gln Thr Lys Leu Asn Tyr Leu Arg Arg Asn Leu
                     -30
                                        -25
 Leu Ile Leu Val Gly Ile Ile Ile Met Val Phe Val Phe Ile Cys Phe
                 -15
                                     -10
 Cys Tyr Leu His Tyr Asn Cys Leu Ser Asp Asp Ala Ser Lys Ala Gly
 Met Val Lys Lys Cly Ile Ala Ala Lys Ser Ser Lys Thr Ser Phe
                        20
 Ser Glu Ala Lys Thr Ala Ser Gln Cys Ser Ser Glu Thr Gln Thr Gly
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 <211> 35
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 <222> -28..-1
<400> 1479
Met Gln Ile Ser Ala Ala Ser Leu Asn Phe Ser Ser Lys Asn Gly Ile
            -25
                            - 20
Phe Phe Ser Leu Thr Leu Ser Gly Cys Lys Phe Ser Lys Leu Leu Cys
        ~10
                            -5
Pro Phe Gly
5
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<222> -52..-1
<400> 1480
Met Ile Phe Glu Pro Val Val Leu Lys Pro Val Phe Leu Asn Ile Phe
                            -45
Phe Phe Ser His His Val Phe Thr Val Phe Phe Ser Gly Ser His Val
    -35
                        -30
                                           -25
Asp Ile Leu Ser Arg Thr Val Leu Val Trp Asp Cys Leu Leu Pro Pro
                    -15
                                       -10
Pro Ser Phe Phe Leu Leu Leu Ser Ser Ser Xaa Ser Xaa Leu Leu
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Leu Xaa Xaa Ser Ser Ser Ser Arg
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<210> 1481
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Met Leu Val Pro Leu Leu Ser His Leu Leu Phe Lys Phe Thr Trp Pro
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WO 99/53051
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-5

Lys Xaa Ser Gln 5

<210> 1482

<211> 70

<212> PRT

<213> Homo sapiens

<220>

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<222> -49..-1

<400> 1482

Met Asp Arg Asn Pro Ser Pro Pro Pro Pro Gly Arg Asp Lys Glu Glu -45 -40 -35

Glu Glu Glu Val Ala Gly Gly Asp Cys Ile Gly Ser Thr Val Tyr Ser -30 -25 -20

Lys His Trp Leu Phe Gly Val Leu Ser Gly Leu Xaa Gln Xaa Val Ser -15 -10 - 5

Pro Gly Lys His Gln Asn Leu Gly Ser Xaa Xaa Glu Glu Gln Leu Thr

Glu Leu Asp Glu Arg Asn

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<211> 37

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -23..-1

<400> 1483

Met Lys Leu Ser Leu Ala Gly Tyr Glu Ile Leu Gly Cys His Phe Phe -20 -15 -10

Ser Leu Ala Leu Leu Asn Thr Gly Pro Gln Tyr Leu Leu Ala Tyr Arg -5 1

Val Ser Ala Glu Arg

10

<210> 1484

<211> 48

<212> PRT

<213> Homo sapiens

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<221> SIGNAL

<222> -40..-1

<400> 1484

Met Ala Thr Ser Val Gly His Arg Cys Leu Gly Leu Leu His Gly Val -35 -30

Ala Pro Trp Arg Ser Ser Leu His Pro Cys Glu Ile Thr Ala Leu Ser -20 -15

Gln Ser Leu Gln Pro Leu Arg Lys Leu Pro Phe Arg Ala Ser Xaa Thr

<210> 1485

<211> 126

<212> PRT

<213> Homo sapiens

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Met Ala Pro Lys Gly Lys Val Gly Thr Arg Gly Lys Lys Gln Ile Phe
                 -45
                                     -40
Glu Glu Asn Arg Glu Thr Leu Lys Phe Tyr Leu Arg Ile Ile Leu Gly
             -30
                                 -25
Ala Asn Ala Ile Tyr Cys Leu Val Thr Leu Val Phe Phe Tyr Ser Ser
         -15
                             -10
Ala Ser Phe Trp Ala Trp Leu Ala Leu Gly Phe Ser Leu Ala Val Tyr
                                         10
Gly Ala Ser Tyr His Ser Met Ser Ser Met Ala Arg Ala Ala Phe Ser
                20
                                     25
Glu Asp Gly Ala Leu Met Asp Gly Gly Met Asp Leu Asn Met Glu Gln
            35
                                40
Gly Met Ala Glu His Leu Lys Asp Val Ile Leu Leu Thr Ala Ile Val
                            55
Gln Val Leu Ser Cys Phe Ser Leu Tyr Val Trp Ser Phe Trp
<210> 1486
<211> 55
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<221> SIGNAL
<222> -29..-1
<400> 1486
Met Ala Ala Val Thr Val Thr Val Thr Lys Thr Ala Ala Ala Ala Thr
                -25
                                     -20
Ala Phe Asn Lys Ala Val Trp Phe Thr Pro Cys Ser Cys Gln Glu Val
           -10
Ser Ser Arg Leu Pro Ala Arg Thr Ala Ala Thr Arg Gln Asp Arg Ala
                        10
Asp Lys Lys Glu Arg Pro Cys
<210> 1487
<211> 34
<212> PRT
<213> Homo sapiens
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<222> -19..-1
<400> 1487
Met Leu Gln Phe Glu Lys Pro Gly Ser Ala Ile Cys Leu Trp His Ser
               -15
                                     -10
Thr Leu Gly Gly Xaa Gly Gly Arg Glu Ile Xaa Ser Leu Arg Pro Ala
Cys Gly
   15
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<222> -18..-1
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Met Leu Ile Ser Tyr Leu Ala Ile Leu Leu Lys Trp Val Ser Asn Ser'
            -15
                               -10
Lys Ser Phe Leu Val Lys Ala Ser
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<400> 1489
Met Lys Leu Gln Thr Leu Ala Phe Trp Ser Ala Tyr Val Pro Cys Gln
                    -10
                                       -5
Thr Gln Asp Arg Asp Ala Pro Arg Leu Thr Leu Glu Gln Ile Asp Leu
                                10
Ile Arg Arg Met Cys Ala Ser Tyr Ser Glu Leu Glu Leu Val Thr Ser
                            25
Ala Lys Ala Leu Asn Asp Thr Gln Lys Leu Ala Cys Leu Ile Gly Val
                       40
                                           45
Glu Gly Gly His Ser Leu Asp Asn Ser Leu Ser Arg
                    55
<210> 1490
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<213> Homo sapiens
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<222> -14..-1
<400> 1490
Met Pro Ala Cys Leu Ser Ser Phe Val Ile Pro Ser Leu Leu Ser Pro
               -10
Ser Ser Pro Pro Ser Ile Gly
  5
<210> 1491
<211> 34
<212> PRT
<213> Homo sapiens
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<222> -16..-1
<400> 1491
Met Val Val Ser Phe Ala Gly Ser Cys Thr Ile Leu Gly Ala Ser Ser
                     -10
His Ser Phe Pro Ile Glu Val Ser Leu Phe Pro Val Asp Cys Gly Phe
            5
Leu Leu
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<221> SIGNAL <222> -34..-1

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 <222> -20..-1
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Met Cys Cys Pro Gly Trp Asn Ala Val Ser Gln Ser Trp Leu Ala Ala
                                        -10
                    -15
 -20
 Pro Ser Thr Ser Trp Val Gln Glu Ile Leu Val Leu Gln Pro Pro Gly
                                5
<210> 1493
<211> 69
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<222> -54..-1
<400> 1493
Met Gly Glu Ile Lys Val Ser Pro Asp Tyr Asn Trp Phe Arg Gly Thr
                -50
                                    -45
                                                        -40
Val Pro Leu Lys Xaa Xaa Xaa Val Asp Asp Asp Ser Lys Ile Trp
            -35
                                -30
                                                    -25
Ser Xaa Tyr Asp Ala Gly Pro Arg Ser Ile Arg Cys Pro Leu Ile Phe
        -20
                            -15
                                                -10
Leu Xaa Xaa Val Ser Gly Thr Xaa Asp Val Phe Phe Arg Gln Ile Leu
 - 5
                                        5
Ala Leu Thr Gly Trp
                15
<210> 1494
<211> 45
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<222> -16..-1
Met Asp Ala Ser His Ser His Leu Ser Leu Val Gly His Ser Arg Ala
                       -10
                                            -5
Cys Gly Val Thr Ser Arg Pro His Ala Arg His Arg Gly Arg Cys Leu
              · 5
                                    10
Gly Pro Cys Ser Arg Ser Gly Pro Arg Leu Cys Ser Ala
<210> 1495
<211> 61
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638 Met Gly Ser Asn Ala Val Val Trp His Thr Lys Pro Ser Leu Leu Asn -30 -25 His Pro Ala Ser Ser Leu Ile Ser His Asp Pro Trp Pro Arg Gly Ala -15 -10 Phe Ala Leu Ser Cys Pro Ser Ala Ser Phe Met Leu Phe Ser Ser Leu 5 Gln Cys Pro Phe Pro Tyr Xaa Xaa Thr Glu Cys Asn Xaa 20 <210> 1496 <211> 56 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1 <400> 1496 Met Lys Glu Asp Gly Ala Cys Leu Phe Arg Ala Val Ala Asp Gln Val -15 -10 -5 Tyr Gly Asp Gln Asp Met His Glu Val Val Arg Lys His Xaa Met Asp 10 Tyr Leu Met Lys Asn Ala Asp Tyr Phe Ser Xaa Tyr Val Thr Glu Asp 20 25 Phe Thr Thr Tyr Ile Xaa Arg Lys 35 <210> 1497 . <211> 24 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 1497 Met Val His Leu Ile Leu Thr Glu Val Leu Ile Met Ile Xaa Glu Ala -15 Xaa Asn Val Trp Cys Gly Asp Ser <210> 1498 <211> 51 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1 <400> 1498 Met Tyr His Asn Leu Phe Ala Leu Leu Leu Ile Asp Ile His Val Val -45 -40 Leu Val Phe Tyr Cys Leu Asp Leu Leu Met Ile His Ile Phe Tyr Cys -25 -20 Lys Tyr Cys Leu Xaa Phe Gly Ile Leu Ala Ser Glu Val Tyr Ser Trp -15 -10 Asn Ile Tyr

<210> 1499 <211> 44

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WO 99/53051
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<212> PRT
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Met Glu Ser Pro Ser Arg Ala Gly Gly Val Xaa Leu Xaa Lys Ala Ala
                                    -20
                                                       -15
Ser Pro Leu Cys Ser Xaa Ser Ser Gly Tyr Cys Xaa Ala Phe Pro Arg
            -10
                                -5
Arg Ser Ala Arg Arg His Leu His Pro Gly His Gly
                        10
<210> 1500
<211> 61
<212> PRT
<213> Homo sapiens
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<222> -25..-1
<400> 1500
Met Trp Arg Tyr Val Ser Arg Leu Ser Ser Val Pro Leu Ile Ser Leu
                    -20
                                       -15
                                                            -10
Ser Val Leu Met Pro Val Gln His Ser Pro Asp Phe Cys Ser Phe Ile
               - 5
                                    1
Val Ser Thr Val Ile Pro Trp Phe Pro Trp Gly Ile Gly Ser Arg Thr
    10
                           15
Leu Met Asp Ile Lys Ile Leu Gly Cys Ser Ser Pro Gly
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                       30
<210> 1501
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<400> 1501
Met Asp Val Ser Cys Lys Ile Leu Tyr Asn Val Ile Glu Lys Phe Cys
                   -25
                                -20
                                                           -15
Asn Asn Leu Leu Lys Leu Ser Ser His Ser Pro Thr Cys Ala Cys Lys
                                    - 5
Leu
<210> 1502
<211> 29
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<213> Homo sapiens
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<222> -20..-1
<400> 1502
Met Ile Phe Lys Asp Val Phe Ser His Leu Ser Gly Ser Ser Leu Gln
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-15

Leu Cys Val Ala Gln Phe Leu Xaa Leu Ser Ala Val Asp

-10

-35

-20

-5

5

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 Met Lys Leu Thr Lys Asn Ile Leu Xaa Val Ile Ile Gly Cys Phe Lys
             -40
 Leu Ile Ala Tyr Lys Asn Ser Val Leu Tyr Phe Tyr Ser Asn Phe Ser
    -25.
 Phe Ser Phe Leu Phe Phe Phe Phe Leu Ser Phe Phe Phe Phe Phe
 Phe Phe
 <210> 1504
 <211> 92
 <212> PRT
 <213> Homo sapiens
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 <222> -87..-1
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<210> 1505 <211> 35 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -17..-1

<400> 1505 Met Ala Asp Ser Leu Glu Ile Lys Leu Pro Phe Leu Pro Phe Ala Gln -10 - 5 Gln Ile Asp Ile Lys Ser Cys Phe Tyr Phe Phe Phe Xaa Asn Xaa Xaa 1 10 Phe Pro Arg

<210> 1506 <211> 115 <212> PRT

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641
 <213> Homo sapiens
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 <222> -35..-1
 <400> 1506
Met Asp Arg Lys Trp Thr Trp Lys Arg Gly Gln Arg Ser His Leu Glu
-35
                     -30
                                         -25
Ser Gly Gln Ala Ala Pro Ala Thr Ala Ala Ala Thr Ala Ala Ser Ala
                -15
                                    -10 .
Thr Thr Gly Ala Ser Val Trp Arg Ser Thr Met Gly Xaa Leu Cys Asp
Cys Thr Xaa Xaa Pro Tyr Glu Gly Pro Phe Cys Lys Lys Glu Val Ser
                         20
Ala Val Phe Glu Ala Gly Thr Ser Val Thr Tyr Met Phe Gln Glu Pro
                    35
                                        40
Tyr Pro Val Thr Lys Asn Ile Ser Leu Ser Ser Ser Ala Ile Tyr Thr
                50
                                    55
Asp Ser Ala Pro Ser Lys Glu Asn Ile Ala Leu Ser Phe Val Thr Thr,
                          70
Gln Ala Pro
        80
<210> 1507
<211> 74
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> '-43..-1
<400>.1507
Met Ala Pro Gln Met Tyr Glu Phe His Leu Pro Leu Ser Pro Glu Glu
           -40
                                -35
Leu Leu Lys Ser Gly Gly Val Asn Gln Tyr Val Val Gln Glu Val Leu
       -25
                            -20
                                                -15
Ser Ile Lys His Leu Pro Pro Gln Leu Arg Ala Phe Gln Ala Ala Phe
   -10
                        - 5
Arg Ala Gln Gly Pro Leu Ala Met Leu Gln His Phe Asp Thr Ile Tyr
               10
Ser Ile Leu His His Phe Arg Ser Ile Asp
<210> 1508
<211> 84
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -15..-1
<400> 1508
Met Ala Ala Val Gln Val Val Gly Ser Trp Pro Ser Val Gln Pro Arg
                    -10
Glu Ala Pro Arg Glu Ala Ile Pro Glu Arg Gly Asn Gly Phe Arg Leu
                                10
Leu Ser Ala Arg Leu Cys Ala Leu Arg Pro Asp Asp Ser Ser Ser Ala
                           25
Arg Thr Glu Ile His Leu Xaa Phe Asp Gln Leu Ile Ser Glu Asn Tyr
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Ser Glu Gly Ser Gly Val Ala Pro Glu Asp Val Ser Ala Leu Leu Val
50 60 65

Gln Ala Cys Gly

<210> 1509

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -30..-1

<400> 1509

Met Phe His Gly Cys His Ile Leu Ser Phe Leu Arg Ile Ser Thr Arg
-30 -25 -20 -15

Gly Phe Leu Phe Phe Leu Gln Phe Ser Phe Pro Leu Tyr Tyr Leu Phe

Arg Xaa Xaa Phe Pro Gln Ser Phe Met Leu Glu Ala Phe Val Arg Cys
5 10 15

<210> 1510

<211> 42

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -26..-1

<400> 1510

Met Tyr Arg His Ser Lys Gln Arg Asn Asn Val Pro Cys Leu Val Leu
-25 -20 -15

Tyr Ala Pro Trp Val Pro Pro Leu Leu Leu Ala Phe Trp Gly Trp Trp -10 -5 1 5

Leu Leu Glu Gln Gly Leu Phe Phe Phe 10

<210> 1511

<211> 137

<212> PRT

<213> Homo sapiens

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<221> SIGNAL

<222> -50..-1

<400> 1511

Met Gly Asp Pro Ser Lys Gln Asp Ile Leu Thr Ile Phe Lys Arg Leu
-50 -45 -40 -35

Arg Ser Val Pro Thr Asn Lys Val Cys Phe Asp Cys Gly Ala Lys Asn

-30 -25 -20
Pro Ser Trp Ala Ser Ile Thr Tyr Gly Val Phe Leu Cys Ile Asp Cys
-15 -10

-15 -10 -5 Ser Gly Ser His Arg Ser Leu Gly Val His Leu Ser Phe Ile Arg Ser

Thr Glu Leu Asp Ser Asn Trp Ser Trp Phe Gln Leu Arg Cys Met Gln 15 20 25 30

Val Gly Gly Asn Ala Ser Ala Ser Ser Phe Phe His Gln His Gly Cys
35
40
45

Ser Thr Asn Asp Thr Asn Ala Lys Tyr Asn Ser Arg Ala Ala Gln Leu
50 55 60

Tyr Arg Glu Lys Ile Lys Ser Leu Ala Ser Gln Ala Thr Arg Lys His

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65
                                               75
Gly Thr Asp Leu Trp Leu Asp Ser Cys
   80
<210> 1512
<211> 26
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<213> Homo sapiens
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<221> SIGNAL
<222> -22..-1
<400> 1512
Met Pro Leu Pro Pro Asn Gln Ser Pro Leu Leu Leu His Leu Val Phe
   -20
                   -15
His Gln Arg Thr Leu Ile Ser Leu Pro Pro
 - 5
<210> 1513
<211> 21
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 1513
Met Phe Leu Thr Phe Phe Phe Cys Thr Gln Val His Gly Pro Ser Ile
   -10
                              - 5
Leu Asp Ser Pro Ala
 5
<210> 1514
<211> 56
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
<400> 1514
Met Val Thr Leu Trp Ile Phe Gln Phe Phe Leu Cys Leu Thr Cys Lys
              -10
                                  - 5
Ala Tyr Asn Leu Arg Asn Cys Asn Asp Gly Lys Gly Xaa Xaa Ser Xaa
                          10
Val Leu Gly Leu Glu Gln Xaa Leu Pro Glu Ser Ala Gly Met Val Xaa
                      25
Phe Leu Gly Leu Lys His Arg Trp
<210> 1515
<211> 37
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -14..-1
<400> 1515
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644
Met Val Leu Trp Ala Gly Pro Xaa Val Pro Leu Leu Cys Ala Ala Xaa
                 -10
                                     - 5
 Gly Leu Gly Ala Leu His Pro Arg Cys Ser Ser Gln Gly Leu Arg Leu
                             10
Ala Xaa Ser Glu Ala
    20
 <210> 1516
 <211> 61
 <212> PRT
 <213> Homo sapiens
<220>
<221> SIGNAL
<222> -41..-1
<400> 1516
Met Asn Trp Arg Arg Lys Ser Val Ile Gly Leu Ser Phe Asp Phe Val
                         -35
Ala Leu Asn Leu Thr Gly Phe Val Ala Tyr Ser Val Phe Asn Ile Gly
                     -20
                                        -15
Leu Leu Trp Val Pro Xaa Xaa Xaa Gly Ala Val Ser Pro Gln Ile Pro
                - 5
Gln Arg Ser Glu Pro Arg Glu Gln Gln Arg Arg Leu Leu
                             15
<210> 1517
<211> 149
<212> PRT
<213> Homo sapiens
<400> 1517
Met Glu Pro Leu Ala Ala Tyr Pro Leu Lys Cys Ser Gly Pro Arg Ala
Lys Val Phe Ala Val Leu Leu Ser Ile Val Leu Cys Thr Val Thr Leu
Phe Leu Leu Gln Leu Lys Xaa Leu Lys Pro Lys Ile Asn Ser Phe Tyr
Ala Phe Glu Val Lys Asp Ala Lys Gly Arg Thr Val Ser Leu Glu Lys
Tyr Lys Gly Lys Val Ser Leu Val Val Asn Val Ala Ser Asp Cys Gln
Leu Thr Asp Arg Asn Tyr Leu Gly Leu Lys Glu Leu His Lys Glu Phe
Gly Pro Ser His Phe Ser Val Leu Ala Phe Pro Cys Asn Gln Phe Gly
            100
Glu Ser Glu Pro Arg Pro Ser Lys Glu Val Glu Ser Phe Ala Arg Lys
Asn Tyr Gly Val Thr Phe Pro Ile Phe His Lys Ile Lys Ile Leu Gly
Ser Glu Gly Glu Leu
145
<210> 1518
<211> 132
<212> PRT
<213> Homo sapiens
<400> 1518
Met Asn Glu Ala Met Ala Thr Asp Ser Pro Arg Arg Pro Ser Arg Cys
                                    10
Thr Gly Gly Val Val Val Arg Pro Gln Ala Val Thr Glu Gln Ser Tyr
                                25
Met Glu Ser Val Val Thr Phe Leu Gln Asp Val Val Pro Gln Ala Tyr
```

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Ser Gly Thr Pro Leu Thr Glu Glu Lys Glu Lys Ile Val Trp Val Arg
                         55
 Phe Glu Asn Ala Asp Leu Asn Asp Thr Ser Arg Asn Leu Glu Phe His
                     70
                                         75
 Glu Ile His Ser Thr Gly Ser Glu Pro Pro Leu Leu Ile Met Ile Gly
                 85
                                     90
 Tyr Ser Asp Gly Met Gln Val Trp Ser Ile Pro Ile Xaa Gly Glu Xaa
             100
                                 105
                                                     110
 Lys Ser Ser Ser Leu Phe Asp Met Ala Gln Phe Glu Arg Leu Glu Ser
        115
                             120
 Cys Leu Leu His
    130
 <210> 1519
 <211> 46
 <212> PRT
<213> Homo sapiens
<400> 1519
Met Pro Val Thr Arg Ala Ser Gln Pro Arg Lys Pro Ser Ser Ala Gln
                                     10
Gln Gln Lys Ala Ala Leu Leu Xaa Asn Asn Thr Ala Leu Gln Ser Val
            20
Ser Leu Arg Ser Lys Thr Thr Ile Arg Glu Arg Pro Ser Ser
<210> 1520
<211> 41
<212> PRT
<213 > Homo sapiens
<400> 1520
Met Asn Gly Phe Gly Arg Leu Glu His Phe Ser Gly Ala Val Tyr Glu
                5
                                    10
Gly Gln Phe Lys Asp Asn Met Phe His Gly Leu Gly Thr Tyr Thr Phe
          20
Pro Asn Gly Ala Lys Tyr Thr Gly Ile
<210> 1521
<211> 131
<212> PRT
<213> Homo sapiens
<400> 1521
Met Ala Lys Ile Ala Lys Thr His Glu Asp Ile Glu Ala Gln Ile Arg
                                   .10
Glu Ile Gln Gly Lys Lys Ala Ala Leu Asp Glu Ala Gln Gly Val Gly
            20
                                25
Leu Asp Ser Thr Gly Tyr Tyr Asp Gln Glu Ile Tyr Gly Gly Ser Asp
                            40
Ser Arg Phe Ala Gly Tyr Val Thr Ser Ile Ala Ala Thr Glu Leu Glu
                       55
Asp Asp Asp Asp Tyr Ser Ser Ser Thr Ser Leu Leu Gly Gln Lys
                    70
                                        75
Lys Pro Gly Tyr His Ala Pro Val Ala Leu Leu Asn Asp Ile Pro Gln
               85
Ser Thr Glu Gln Tyr Asp Pro Phe Ala Glu His Arg Pro Pro Lys Ile
           100
                                105
                                                    110
Ala Asp Arg Glu Asp Glu Tyr Lys Lys His Arg Arg Thr Met Ile Ile
Ser Gln Ser
   130
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<210> 1522 <211> 82

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<212> PRT
 <213> Homo sapiens
 <400> 1522
Met Pro Ile Asn Lys Ser Glu Lys Pro Glu Ser Cys Asp Asn Val Lys
                                     10
Val Val Val Arg Cys Arg Pro Leu Asn Glu Arg Glu Lys Ser Met Cys
             20
                                 25
Tyr Lys Gln Ala Val Ser Val Asp Glu Met Arg Gly Thr Ile Thr Val
         35
                             40
His Lys Thr Asp Ser Ser Asn Glu Pro Pro Lys Thr Phe Thr Phe Asp
                        55
Thr Val Phe Gly Pro Glu Ser Lys Gln Leu Asp Val Tyr Asn Leu Thr
65
                    70
Ala Arg
<210> 1523
<211> 40
<212> PRT
<213> Homo sapiens
<400> 1523
Met Pro Asn Arg Gly Gly Asn Gly Leu Ala Pro Gly Glu Asp Arg Phe
Lys Pro Val Val Pro Trp Pro His Val Glu Gly Val Glu Val Asp Leu
            20
                                25
Glu Ser Ile Arg Arg Ile Asn Lys
<210> 1524
<211> 35
<212> PRT
<213> Homo sapiens
<400> 1524
Met Ser Leu Trp Leu Cys Phe Gln Cys Pro Leu Gly Val Ser Lys Ser
                                    10
Asn Lys Lys Arg Ile Asn Leu Cys Asn Gly Phe Trp Asn Glu Lys Ile
            20
Lys Asn Arg
      35
<210> 1525
<211> 47
<212> PRT
<213> Homo sapiens
<400> 1525
Met Gly Thr His Val Phe Ala Ile Asn Lys Arg Thr Tyr Val Ile Ser
Arg Asp Arg Glu Leu Ser Thr Ala Lys Pro Xaa Cys Ser Ser Leu Leu
            20
Thr Ala Pro Val Leu Cys Tyr Trp Arg Ala Cys Pro Leu Gln Thr
<210> 1526
<211> 56
<212> PRT
<213> Homo sapiens
<400> 1526
Met Phe Cys Phe Leu Phe Ser Trp Trp Leu Arg Gly Gly Leu His Val
                                    10
Leu Leu Asn Thr Cys Leu Tyr Val Pro Tyr Gly Tyr Leu Ser Leu Ile
           20
                                25
Cys Leu Leu Cys Leu Trp Tyr Leu Asn Leu Tyr Lys Phe Ser Ile Phe
```

Phe Ser Phe Leu Ser Phe Phe Phe

WO 99/53051 647 50 55 <210> 1527 <211> 55 <212> PRT <213> Homo sapiens <400> 1527 Met Thr Thr Ser Lys His Ala Ala Tyr Cys Leu Lys Gly Ser Cys Leu Xaa Gln Ala Arg Val Gln Trp Pro Leu Lys Xaa Thr Thr Ala Ser 25 Asn Phe Trp Ala Gln Val Ile Leu Ser Leu Pro Val Val Phe Val Asp . 35 Cys Leu Met Glu Xaa His Gly 50 <210> 1528 <211> 121 <212> PRT <213> Homo sapiens <400> 1528 Met Glu Gly Gly Gly Ile Pro Leu Glu Thr Leu Lys Glu Glu Ser 10 Gln Ser Arg His Val Leu Pro Ala Ser Phe Glu Val Asn Ser Leu Gln Lys Ser Asn Trp Gly Phe Leu Leu Thr Gly Leu Val Gly Gly Thr Leu Val Ala Val Tyr Ala Val Ala Thr Pro Phe Val Thr Pro Ala Leu Arg Lys Val Cys Leu Pro Phe Val Pro Ala Thr Met Lys Gln Ile Glu Asn Val Val Lys Met Leu Arg Cys Arg Arg Gly Ser Leu Val Asp Ile Gly 90 Ser Gly Asp Gly Arg Ile Val Ile Ala Ala Ala Lys Lys Gly Phe Xaa 100 105 110 Ala Val Gly Tyr Glu Leu Asn Pro Trp 115 <210> 1529 <211> 154 <212> PRT <213> Homo sapiens

<400> 1529

Met Ala Thr Pro Leu Ala Val Asn Ser Ala Ala Ser Leu Trp Gly Pro Tyr Lys Asp Ile Trp His Lys Val Gly Asn Ala Leu Trp Arg Arg Gln 20

Pro Glu Ala Val Xaa Leu Leu Asp Lys Ile Leu Lys Lys His Lys Pro

Asp Phe Ile Ser Leu Phe Lys Asn Pro Pro Lys Asn Val Gln Gln His 55

Glu Lys Val Gln Lys Ala Ser Thr Glu Gly Val Ala Ile Gln Gly Gln 70

Gln Gly Thr Arg Leu Leu Pro Glu Gln Leu Ile Lys Glu Ala Phe Ile

Leu Ser Asp Leu Phe Asp Ile Gly Glu Leu Ala Ala Val Glu Leu Leu 105

Leu Ala Gly Glu His Gln Gln Pro His Phe Pro Gly Leu Thr Arg Gly 120

Leu Val Ala Val Leu Leu Tyr Trp Asp Gly Lys Arg Cys Ile Ala Asn 135

Ser Leu Lys Ala Leu Ile Gln Ser Arg Arg

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<210> 1530
 <211> 125
 <212> PRT
 <213> Homo sapiens
 <400> 1530
 Met Asn Gly Arg Ala Asp Phe Arg Glu Pro Asn Ala Glu Val Pro Arg
                                     10
                                                          15
 Pro Ile Pro His Ile Gly Pro Asp Tyr Ile Pro Thr Glu Glu Glu Arg
 Arg Val Phe Ala Glu Cys Asn Asp Glu Ser Phe Trp Phe Arg Ser Val
 Pro Leu Ala Ala Thr Ser Met Leu Ile Thr Gln Gly Leu Ile Ser Lys
 Gly Ile Leu Ser Ser His Pro Lys Tyr Gly Ser Ile Pro Lys Leu Ile
                     70
Leu Ala Cys Ile Met Gly Tyr Phe Ala Gly Lys Leu Ser Tyr Val Lys
                 85
Thr Cys Gln Glu Lys Phe Lys Lys Leu Glu Asn Ser Pro Leu Gly Glu
            100
                                 105
Ala Leu Arg Ser Gly Gln Ala Arg Arg Ser Ser Pro Pro
                             120
<210> 1531
<211> 35
<212> PRT
<213> Homo sapiens
<400> 1531
Met His Met Ser Lys Leu Ile Asn Leu Tyr Thr Ser Xaa Met Cys Asn
                                    10
Leu Leu Xaa Ile His Leu Xaa Xaa Ile Ser Cys Leu Xaa Asn Asn Lys
Xaa Thr Leu
    35
<210> 1532
<211> 111
<212> PRT
<213> Homo sapiens
<400> 1532
Met Tyr Gly Lys Gly Lys Ser Asn Ser Ser Ala Val Pro Ser Asp Ser
                                    10
Gln Ala Arg Glu Lys Leu Ala Leu Tyr Val Tyr Glu Tyr Leu Leu His
                                25
Val Gly Ala Gln Lys Ser Ala Gln Thr Phe Leu Ser Glu Ile Arg Trp
                            40
Glu Lys Asn Ile Thr Leu Gly Glu Pro Pro Gly Phe Leu His Ser Trp
                        55
Trp Cys Val Phe Trp Asp Leu Tyr Cys Ala Ala Pro Glu Arg Arg Glu
                    70
Thr Cys Glu His Ser Ser Glu Ala Lys Ala Phe His Asp Tyr Ser Ala
                85
                                    90
Ala Ala Ala Pro Ser Pro Val Leu Gly Asn Ile Pro Pro Gly Asp
<210> 1533
<211> 107
<212> PRT
<213> Homo sapiens
<400> 1533
Met Asn Pro Glu Tyr Asp Tyr Leu Phe Lys Leu Leu Leu Ile Gly Asp
                                    10
Ser Gly Val Gly Lys Ser Cys Leu Leu Leu Arg Phe Ala Asp Asp Thr
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649
             20
                                  25
 Tyr Thr Glu Ser Tyr Ile Ser Thr Ile Gly Val Asp Phe Lys Ile Arg
 Thr Ile Glu Leu Asp Gly Lys Thr Ile Lys Leu Gln Ile Trp Asp Thr
 Ala Gly Gln Glu Arg Phe Arg Thr Ile Thr Ser Ser Tyr Tyr Arg Gly
                     70
                                        . 75
Ala His Gly Ile Ile Val Val Tyr Asp Val Thr Asp Gln Glu Ser Tyr
                 85
 Ala Xaa Val Lys Gln Trp Leu Gln Glu Ile Asp
 <210> 1534
<211> 31
<212> PRT
<213> Homo sapiens
<400> 1534
Met Asn Ser Lys Ala Xaa Lys Ser Ser Thr Ala Asn Gln Gly Asp Gly
                                  . 10
Asp Glu Glu Xaa Val Gly Arg Xaa Glu Xaa Ser Val Gly Glu Phe
                                 25
<210> 1535
<211> 48
<212> PRT
<213> Homo sapiens
Met Leu Tyr Ser Thr Leu Lys His Thr Leu Gln Tyr Val Ile Ile Asn
                                     10
Cys Gly His His Ala Val Gln Lys Ile Ser Lys Thr Tyr Ser Ser Cys
           20
                                25
Leu Thr Glu Xaa Leu Tyr Pro Leu Pro Asn Ile Ser Pro Ile Pro Pro
        35
<210> 1536
<211> 94
<212> PRT
<213> Homo sapiens
<400> 1536
Met Asn Asp Glu Val Asn Pro Arg Arg Val Leu Glu Leu Met Gly Ser
                                    10
Glu Val Thr Gln Ile Ala Cys Gly Arg Gln His Thr Leu Xaa Phe Val
                                25
Pro Ser Ser Gly Leu Ile Tyr Ala Phe Gly Cys Gly Ala Arg Gly Gln
                            40
Leu Gly Thr Gly His Thr Cys Asn Val Lys Cys Pro Ser Pro Val Lys
Gly Tyr Trp Ala Ala His Ser Gly Gln Leu Ser Ala Arg Ala Asp Arg
                    70
Phe Lys Tyr His Ile Val Lys Gln Ile Phe Ser Gly Gly Asp
                85
<210> 1537
<211> 22
<212> PRT
<213> Homo sapiens
Met Pro Val Arg Thr Ile Thr Arg Gln Asn Gly Ser Val Pro Trp Gly
               5
                                    10
Pro Asn His Cys Asp Lys
           20
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<211> 94
  <212> PRT
  <213> Homo sapiens
  <400> 1538
  Met Gly Asp Asn Pro Phe Gln Pro Lys Ser Asn Ser Lys Met Ala Glu
  Leu Phe Met Glu Cys Glu Glu Glu Leu Glu Pro Trp Gln Lys Lys
              20
  Val Lys Glu Val Glu Asp Asp Asp Asp Glu Pro Ile Phe Val Gly
                              40
  Glu Ile Ser Ser Ser Lys Pro Ala Ile Ser Asn Ile Leu Asn Arg Val
                          55
 Asn Pro Ser Ser Tyr Ser Arg Gly Leu Lys Asn Gly Ala Leu Ser Arg
 Gly Ile Thr Ala Ala Phe Lys Pro Thr Ser Gln His Tyr Thr
                 85
 <210> 1539
 <211> 67
 <212> PRT
 <213> Homo sapiens
 <400> 1539
 Met Val Thr Gln Ala Gln Gln Glu Ile Thr Val Gln Gln Leu Met Ala
 His Leu Asp Ala Ile Arg Lys Asp Met Val Ile Leu Glu Lys Ser Glu
             20
                                 25
 Phe Ala Asn Leu Arg Ala Glu Asn Glu Lys Met Lys Ile Glu Leu Asp
                             40 .
 Gln Val Lys Gln Gln Leu Met His Glu Thr Ser Xaa Ile Arg Ala Asp
                        55
 Asn Lys Leu
 <210> 1540
 <211> 38
 <212> PRT
 <213> Homo sapiens
 <400> 1540
Met Lys Phe Gly Asn Val Arg Met Xaa Ser Ile Gln Ile Phe Ile Val
                                    10
Ser Ile Trp Ser Phe Phe Leu Phe Tyr Gly Lys Tyr Thr Tyr Ile Arg
                                25
Leu Ile Leu Ser Gln Gly
        35
<210> 1541
<211> 35
<212> PRT
<213> Homo sapiens
<400> 1541
Met Thr Phe Asp Leu Ser Val Phe Ser Thr Leu Ser Asp His Phe Tyr
                                    10
Ser Ser Ser Leu Ser Asn Thr Ala Arg Asn Leu Tyr Ile Cys Leu Phe
                                25
His Ile Thr
        35
<210> 1542
<211> 28
<212> PRT
<213> Homo sapiens
<400> 1542
Met Gly Arg Trp Ala Leu Asp Val Ala Phe Leu Trp Lys Ala Val Leu
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10
                                                          15
 Thr Leu Gly Leu Val Leu Leu Tyr Tyr Cys Phe Ser
              20
  <210> 1543
  <211> 128
  <212> PRT
 <213> Homo sapiens
 <400> 1543
 Met Ala Leu His Val Pro Lys Ala Pro Gly Phe Ala Gln Met Leu Lys
 Glu Gly Ala Lys His Phe Ser Gly Leu Glu Glu Ala Val Tyr Arg Asn
 Ile Gln Ala Cys Lys Glu Leu Ala Gln Thr Thr Arg Thr Ala Tyr Gly
 Pro Asn Gly Met Asn Lys Met Val Ile Asn His Leu Glu Lys Leu Phe
                          55
 Val Thr Asn Asp Ala Ala Thr Ile Leu Arg Glu Leu Glu Val Gln His
 Pro Ala Ala Lys Met Ile Val Met Ala Ser His Met Gln Glu Gln Glu
                 85
 Val Gly Asp Gly Thr Asn Phe Val Leu Val Phe Ala Gly Ala Leu Leu
                                 105
 Glu Leu Ala Glu Glu Leu Leu Arg Ile Gly Leu Ser Val Ser Glu Val
                             120
 <210> 1544
 <211> 33
 <212> PRT
 <213> Homo sapiens
 <400> 1544
Met Ala Asn Arg Tyr Thr Met Asp Leu Thr Ala Ile Tyr Glu Ser Leu
                5
Leu Ser Leu Ser Pro Asp Val Thr Leu Thr His Phe Ala His Cys Asn
                                 25
Leu
<210> 1545
<211> 68
<212> PRT
<213> Homo sapiens
<400> 1545
Met Met Glu Glu Ser Gly Ile Glu Thr Thr Pro Pro Gly Thr Pro Pro
                                     10
Pro Asn Pro Ala Gly Leu Ala Ala Thr Ala Met Ser Ser Thr Pro Val
                                25
Pro Leu Ala Ala Thr Ser Ser Phe Ser Ser Pro Asn Val Ser Ser Met
                             40
Glu Ser Phe Pro Pro Leu Ala Tyr Ser Thr Pro Gln Pro Pro Leu Pro
                        55
Pro Val Arg Pro
<210> 1546
<211> 50
<212> PRT
<213> Homo sapiens
<400> 1546
Met Leu Cys Leu Thr Glu Gly Ala Lys Asp Glu Cys Asn Val Val Glu
Val Val Ala Arg Asn His Asp His Gln Glu Ile Ala Val Pro Val Ala
Xaa Leu Lys Leu Ser Cys Gln Pro Met Leu Ser Leu Asp Asp Phe Gln
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35 40 45 Leu Gln

50 <210> 1547

<211> 139

<212> PRT

<213> Homo sapiens

<400> 1547

Met Pro Thr Val Ser Val Lys Arg Asp Leu Leu Phe Gln Ala Leu Gly
1 5 10 15

Arg Thr Tyr Thr Asp Glu Glu Phe Asp Glu Leu Cys Phe Glu Phe Gly 20 25 30

Leu Glu Leu Asp Glu Ile Thr Ser Glu Lys Glu Ile Ile Ser Lys Glu 35

Gln Gly Asn Val Lys Ala Ala Gly Ala Ser Asp Val Val Leu Tyr Lys
50 55 60

Ile Asp Val Pro Ala Asn Arg Tyr Asp Leu Leu Cys Leu Glu Gly Leu 65 70 75 80

Val Arg Gly Leu Gln Val Phe Lys Glu Arg Ile Lys Ala Pro Val Tyr,

Lys Arg Val Met Pro Asp Gly Lys Ile Gln Lys Leu Ile Ile Thr Glu
100 105 110

Glu Thr Ala Lys Ile Arg Pro Phe Ala Val Ala Ala Val Leu Arg Asn 115 120 125

Ile Lys Phe Thr Lys Asp Arg Tyr Asp Ser Phe 130 135

<210> 1548

<211> 71

<212> PRT

<213> Homo sapiens

<400> 1548

Met Phe Ser Glu Glu Leu Trp Leu Glu Asn Glu Lys Lys Cys Ala Val 1 5 10 15

Val Arg Lys Ser Lys Gln Gly Arg Lys Arg Gln Glu Leu Leu Ala Val 20 25 30

Ala Phe Gly Val Lys Val His Thr Phe Arg Gly Pro His Trp Cys Glu
35 40 45

Tyr Cys Ala Asn Phe Met Trp Gly Leu Ile Ala Gln Gly Val Arg Cys
50 55 60

Ser Asp Cys Gly Leu Asn Val

<210> 1549

<211> 29

<212> PRT

<213 > Homo sapiens

<400> 1549

Met Val Val Phe Met Thr Tyr Val Thr Leu Pro Phe Phe Phe Ser Phe l 5 10 15

Ile Ser Ser Leu Leu Ser Phe Phe Phe Leu Phe Leu Leu

20 2:

<210> 1550

<211> 50

<212> PRT

<213> Homo sapiens

20

<400> 1550

Met Gln Glu Leu Phe Leu Lys Phe Val Asp Glu Asn Trp Glu Gly Ser 1 5 10 15

Leu Lys Ser Lys Tyr Val Arg Gly Ser Asp Pro Val Leu Lys Leu Leu

Asp Asp Asn Gly Asn Ile Ala Glu Glu Leu Ser Ile Leu Lys Trp Thr 35 40

Gln Thr 50

<210> 1551

<211> 68

<212> PRT

<213> Homo sapiens

<400> 1551

Met Pro Lys Thr Met His Phe Leu Phe Arg Phe Ile Val Phe Phe Tyr

1 10 15

Leu Trp Gly Leu Phe Thr Ala Gln Arg Gln Lys Lys Glu Glu Ser Thr
20 25 30

Glu Glu Val Lys Ile Glu Val Leu His Arg Pro Glu Asn Cys Ser Lys

Thr Ser Lys Lys Gly Asp Leu Leu Asn Ala His Tyr Asp Gly Tyr Leu
50 55 60

Ala Lys Asp Gly

65

<210> 1552

<211> 52

<212> PRT

<213> Homo sapiens

<400> 1552

Met Leu Glu Glu Leu Lys Ala Gly Gln Glu Leu Glu Glu Gln Thr Ile
1 5 10 15

Ser His Gly Phe Ala Arg Gly Val Arg Arg Gly Val Ala Ile Val Gly 20 25 30

Lys Gly Leu Glu Trp His Gly Cys Trp Trp Met Cys His Gly Tyr Arg
35 40 45

Ile Leu Ala Gly

<210> 1553

<211> 37

<212> PRT

<213> Homo sapiens

<400> 1553

Met Arg Leu Gly Ser Ser Lys Leu Lys Ser Asn Gln Leu Leu Gln Glu 1 5 10

Ala Leu Ser Arg Met Lys Trp Gly Gly Pro Ser Phe Gln Pro Arg Lys 20 25 30

Pro Thr Val Pro Gly

35 .

<210> 1554

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -13..-1

<400> 1554

Met Leu Leu Leu Leu Leu Leu Pro Leu Ala Leu Gly Asp Lys Gly
-10 -5 1

Asp Gly Gly Arg Gln Thr Ile Trp Gly Trp Leu Leu Ala Ala Ser Ala 5 10 15

Gly Ala Gly Asp Gly Ala Gly Gly Pro Val Cys Pro Cys Ala Leu Leu 20 25 30 35 Leu Leu Pro Pro Gly Trp Leu Asp

<210> 1555

<211> 95 <212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -18..-1

<400> 1555

Met Lys Leu Leu Met Val Leu Met Leu Ala Ala Leu Leu Leu His Cys

Tyr Ala Asp Ser Gly Cys Lys Leu Leu Glu Asp Met Val Glu Lys Thr

Ile Asn Ser Asp Ile Ser Ile Pro Glu Tyr Lys Glu Leu Leu Gln Glu
15 20 25 30

Phe Ile Asp Ser Asp Ala Ala Ala Glu Ala Met Gly Lys Phe Lys Glm
35 40 45

Cys Phe Leu Asn Gln Ser His Arg Thr Leu Lys Asn Phe Gly Leu Met

Met His Thr Val Tyr Asp Ser Ile Trp Cys Asn Met Lys Ser Asn 65

<210> 1556

<211> 95

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -31..-1

<400> 1556

Met Val Ala Met Ala Ala Gly Pro Ser Gly Cys Leu Val Pro Ala Phe
-30 -25 -20

Gly Leu Arg Leu Leu Leu Ala Thr Val Leu Gln Ala Val Ser Ala Phe
-15 -5 1

Gly Ala Glu Phe Ser Ser Glu Ala Cys Arg Glu Leu Gly Phe Ser Ser

Asn Leu Cys Ser Ser Cys Asp Leu Leu Gly Gln Phe Asn Leu Leu 20 25 30

Gln Leu Asp Pro Asp Cys Arg Gly Cys Cys Gln Glu Glu Ala Gln Phe 35 40 45

Glu Thr Lys Lys Leu Tyr Ala Gly Ala Ile Leu Glu Val Cys Gly 50 60

<210> 1557

<211> 101

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -32..-1

<400> 1557

Met Phe Ala Pro Ala Val Met Arg Ala Phe Arg Lys Asn Lys Thr Leu
-30 -25 -20

Gly Tyr Gly Val Pro Met Leu Leu Leu Ile Val Gly Gly Ser Phe Gly
-15 -5

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Leu Arg Glu Phe Ser Gln Ile Arg Tyr Asp Ala Val Lys Ser Lys Met
Asp Pro Glu Leu Glu Lys Lys Leu Lys Glu Asn Lys Ile Ser Leu Glu
 Ser Glu Tyr Glu Lys Ile Lys Asp Ser Lys Phe Asp Asp Trp Lys Asn
 Ile Arg Gly Pro Arg Pro Trp Glu Asp Pro Asp Leu Leu Gln Gly Lys
Lys Ser Arg Lys Pro
65
<210> 1558
<211> 115
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -51..-1
<400> 1558
Met Gln Ala Gln Ala Pro Val Val Val Thr Gln Pro Gly Val Gly
    -50
                        -45
Pro Gly Pro Ala Pro Gln Asn Ser Asn Trp Gln Thr Gly Met Cys Asp
                    -30
Cys Phe Ser Asp Cys Gly Val Cys Leu Cys Gly Thr Phe Cys Phe Pro
                -15
Cys Leu Gly Cys Gln Val Ala Ala Asp Met Asn Glu Cys Cys Leu Cys
Gly Thr Ser Val Ala Met Arg Thr Leu Tyr Arg Thr Arg Tyr Gly Ile
Pro Gly Ser Ile Cys Asp Asp Tyr Met Ala Thr Leu Cys Cys Pro His
Cys Thr Leu Cys Gln Ile Lys Arg Asp Ile Asn Arg Arg Ala Met
                50
                                    55.
Arg Thr Phe
<210> 1559
<211> 126
<212> PRT
<213> Homo sapiens
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<400> 1559
Met Asp Lys Ser Leu Leu Leu Glu Leu Pro Ile Leu Leu Cys Cys Phe
               -20
                                    -15
Arg Ala Leu Ser Gly Ser Leu Ser Met Arg Asn Asp Ala Val Asn Glu
Ile Val Ala Val Lys Asn Asn Phe Pro Val Ile Glu Ile Val Arg Cys
Arg Met Cys His Leu Gln Phe Pro Gly Glu Lys Cys Ser Arg Gly Arg
Gly Ile Cys Thr Ala Thr Thr Glu Glu Ala Cys Met Val Gly Arg Met
Phe Lys Arg Asp Gly Asn Pro Trp Leu Thr Phe Met Gly Cys Leu Lys
Asn Cys Ala Asp Val Lys Gly Ile Arg Trp Ser Val Tyr Leu Val Asn
                           80
Phe Arg Cys Xaa Arg Ser His Asp Leu Cys Asn Glu Asp Leu
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35

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<210> 1560
  <211> 102
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -16..-1
  <400> 1560
 Met Asp Leu Leu Trp Ile Leu Pro Ser Leu Trp Leu Leu Leu Gly
                          -10
 Gly Pro Ala Cys Leu Lys Thr Gln Glu His Pro Ser Cys Pro Gly Pro
                                      10
 Arg Glu Leu Glu Ala Ser Lys Val Val Leu Leu Pro Ser Cys Pro Gly
 Ala Pro Gly Ser Pro Gly Glu Lys Gly Ala Pro Gly Pro Gln Gly Pro
 Pro Gly Pro Pro Gly Lys Met Gly Pro Lys Gly Glu Pro Gly Asp Pro
                         55
                                              60
 Val Asn Leu Leu Arg Cys Gln Glu Gly Pro Arg Asn Cys Arg Glu Leu
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 Leu Ser Arg Ala Pro Pro
 <210> 1561
 <211> 60
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
 <222> -19..-1
 <400> 1561
Met Glu Ser Pro Ser Xaa Ser Ala Val Val Leu Pro Ser Thr Pro Gln
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                                     -10
Ala Ser Ala Asn Pro Ser Ser Pro Tyr Thr Asn Ser Ser Arg Lys Gln
Pro Met Ser Ala Thr Leu Arg Glu Arg Leu Arg Lys Thr Arg Phe Ser
                        20
Phe Asn Ser Ser Xaa Asn Val Val Asn Val Leu Lys
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<210> 1562
<211> 97
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -16..-1
<400> 1562
Met Asp Phe Trp Leu Trp Pro Leu Tyr Phe Leu Pro Val Ser Gly Ala
   -15
                        -10
Leu Arg Ile Leu Pro Glu Val Lys Val Glu Gly Glu Leu Gly Gly Ser
                                    10
Val Thr Ile Lys Cys Pro Leu Pro Glu Met His Val Arg Ile Tyr Leu
           20
                               25
Cys Arg Glu Met Ala Gly Ser Gly Thr Cys Gly Thr Val Val Ser Thr
```

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657
  Thr Asn Phe Ile Xaa Ala Glu Tyr Lys Gly Arg Val Thr Leu Arg Ala
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  Ile Pro Thr Gln Glu Ser Val Pro Ser Gly Gly Asn Thr Ala Asp Arg
                      70
                                           75
  Lys
  <210> 1563
  <211> 82
  <212> PRT
  <213> Homo sapiens
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  <221> SIGNAL
  <222> -34..-1
  <400> 1563
 Met Val Gly Glu Ala Gly Arg Asp Leu Arg Arg Arg Ala Val Ala
                                      -25
 Val Thr Ala Glu Lys Met Ala Val Leu Ala Pro Leu Ile Ala Leu Val
                                  -10
 Tyr Ser Xaa Pro Arg Leu Ser Arg Trp Leu Ala Gln Pro Tyr Tyr Leu
                                              10
 Leu Ser Xaa Leu Leu Ser Xaa Ala Phe Leu Leu Val Arg Xaa Leu Pro
                     20
                                         25
 Pro Leu Cys His Gly Leu Pro Thr Gln Arg Glu Xaa Gly Asn Pro Ser
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                                                          45
 Xaa Xaa
 <210> 1564
 <211> 48
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 <213> Homo sapiens
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 <221> SIGNAL
 <222> -17..-1
 <400> 1564
Met Ala Gln Leu Trp Leu Ser Cys Phe Leu Leu Pro Ala Leu Val Val
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        -15
                                                 -5
Ser Val Ala Ala Asn Val Ala Pro Xaa Phe Leu Ala Asn Met Thr Ser
Val Ile Leu Pro Glu Asp Cys Leu Trp Val Pro Arg Pro Ser Gly Trp
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                                     25
<210> 1565
<211> 105
<212> PRT
<213> Homo sapiens
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<221> SIGNAL
<222> -34..-1
<400> 1565
Met Val Gly Glu Ala Gly Arg Asp Leu Arg Arg Arg Ala Val Ala
                -30
                                    -25
                                                         -20
Val Thr Ala Glu Lys Met Ala Val Leu Ala Pro Leu Ile Ala Leu Val
            -15
                                -10
Tyr Ser Val Pro Arg Leu Ser Arg Trp Leu Ala Gln Pro Tyr Tyr Leu
                                            10
Leu Ser Ala Leu Leu Ser Ala Ala Phe Leu Leu Val Arg Lys Leu Pro
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15

<210> 1566 <211> 88 <212> PRT <213> Homo sapiens

<220>
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<222> -19. -1

<400> 1566

 Met
 Val
 Ala
 Trp
 Arg
 Ser
 Ala
 Phe
 Leu
 Val
 Cys
 Leu
 Ala
 Phe
 Ser
 Leu

 Ala
 Thr
 Leu
 Val
 Gly
 Ser
 Gly
 Asp
 Phe
 A

<210> 1567 <211> 119 <212> PRT <213> Homo sapiens

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<220>
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<222> -53..-1

<400> 1567

Met Ala Asp Pro Asp Pro Arg Tyr Pro Arg Ser Ser Ile Glu Asp Asp -40

Phe Asn Tyr Gly Ser Ser Val Ala Ser Ala Thr Val His Ile Arg Met -35

Ala Phe Leu Arg Lys Val Tyr Ser Ile Leu Ser Leu Gln Val Leu Leu -20

Thr Thr Val Thr Ser Thr Val Phe Leu Tyr Phe Glu Ser Val Arg Thr

Phe Val His Glu Ser Pro Ala Leu Ile Leu Leu Phe Ala Leu Gly Ser

15 20 25

Leu Gly Leu Ile Phe Ala Leu Xaa Leu Asn Arg His Lys Tyr Pro Leu 30 35 40

Asn Leu Tyr Leu Leu Phe Gly Phe Thr Leu Leu Glu Ala Leu Thr Val

Ala Val Val Thr Val Leu 60 65

<210> 1568 <211> 104 <212> PRT

<213> Homo sapiens

<221> SIGNAL <222> -55..-1

<400> 1568

Met Ser Ser Gln Lys Gly Asn Val Ala Arg Ser Arg Pro Gln Lys His -50 -45 Gln Asn Thr Phe Ser Phe Lys Asn Asp Lys Phe Asp Lys Ser Val Gln -35 -30 -25 Thr Lys Ser Met Asn Asn Leu Ser Phe Ser Glu Leu Cỳs Cys Leu Phe -15 Cys Cys Pro Pro Cys Pro Gly Lys Ile Ala Ser Lys Leu Ala Phe Leu Pro Pro Asp Pro Thr Tyr Thr Leu Met Cys Asp Glu Ser Gly Ser Val 15 20 Gly Leu Tyr Ile Cys Leu Asn Glu Gln Thr Gly Ser Ile Leu Leu Glu 30 35

Lys Lys Met Leu Leu Ser Val Ser 45

<210> 1569

<211> 126

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -62..-1

<400> 1569

Met Arg Asn Lys Lys Ile Leu Lys Glu Asp Glu Leu Leu Ser Glu Thr
-60 -55 -55 -50

Gln Gln Ala Ala Phe His Gln Ile Ala Met Glu Pro Phe Glu Ile Asn
-45 -35

Val Pro Lys Pro Lys Arg Asn Gly Val Asn Phe Ser Leu Ala Val
-30 -25 -20 -15

Val Val Ile Tyr Leu Ile Leu Leu Thr Ala Gly Ala Gly Leu Leu Val

Val Gln Val Leu Asn Leu Gln Ala Arg Leu Arg Val Leu Glu Met Tyr

5 10 15

Phe Leu Asn Asp Thr Leu Ala Ala Glu Asp Ser Pro Ser Phe Ser Leu 20 25 30

Leu Gln Ser Ala His Pro Gly Glu His Leu Ala Gln Gly Ala Ser Arg

Leu Gln Ser Cys Arg Pro Asn Ser Pro Gly Ser Ala Ser Xaa

<210> 1570

<211> 134

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -56..-1

<400> 1570

Met Ala Pro Thr Lys Pro Ser Phe Gln Gln Asp Pro Ser Arg Arg Glu
-55 -50 -45

Arg Leu Gln Ala Leu Arg Lys Glu Lys Ser Arg Asp Ala Ala Arg Ser
-40
-35
-30

Arg Arg Gly Lys Glu Asn Phe Glu Phe Tyr Glu Leu Ala Lys Leu Leu -20 -15 -10

Pro Leu Pro Ala Ala Ile Thr Ser Gln Leu Asp Lys Ala Ser Ile Ile

```
- 5
  Arg Leu Thr Ile Ser Tyr Leu Lys Met Arg Asp Phe Ala Asn Gln Gly
                          15
  Asp Pro Pro Trp Asn Leu Arg Met Glu Gly Pro Pro Pro Asn Thr Ser
                      30
                                          35
  Val Lys Val Ile Gly Ala Gln Arg Arg Arg Ser Pro Ser Ala Leu Ala
                                     50
                                                         .55
  Ile Glu Val Phe Glu Ala His Leu Gly Ser His Ile Leu Gln Ser Trp
                                 65
                                                70
   Met Ala Leu Tyr Leu His
          75
  <210> 1571
  <211> 28
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -20..-1
  <400> 1571
  Met Glu Glu Leu Gln Asp Gln Ala Leu Leu Ser Val Cys Ser Thr Asp
  -20
                 -15
                                         -10
  Val Thr Thr Ala His Ala Trp Leu Thr Val Leu Val
  <210> 1572
 <211> 28
  <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -20..-1
 <400> 1572
 Met Glu Glu Leu Gln Asp Gln Ala Leu Leu Ser Val Cys Ser Thr Asp
                    -15
                                        -10
 Val Thr Thr Ala His Ala Trp Leu Thr Val Leu Val
                                 5
 <210> 1573
 <211> 47
 <212> PRT
. <213 > Homo sapiens
 <220>
 <221> SIGNAL
 <222> -45..-1
 <400> 1573
 Met Val Gly Arg Val Arg Val Cys Arg Lys Tyr Pro Pro Thr Thr Leu
                   -40
                                   -35
 Trp Glu Gly Ala Arg Gly His Arg Gln Ile Ser Val Ser Pro Trp Asn
                -25
                                    -20
                                                     -15
 Ile Cys Cys Ala Ala Ala Ala Ala Ala Ala Gly Ser Arg Ile
                                - 5
 <210> 1574
 <211> 137
 <212> PRT
 <213> Homo sapiens
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  <221> SIGNAL
  <222> -52..-1
  <400> 1574 .
 Met Lys Arg Leu Glu Ala Lys Tyr Ala Pro Leu His Leu Val Pro Leu
          -50
                             -45
 Ile Glu Arg Leu Gly Thr Pro Gln Gln Ile Ala Ile Ala Arg Glu Gly
 Asp Leu Leu Thr Lys Glu Arg Leu Cys Cys Gly Leu Ser Met Phe Glu
 -20
                      -15
                                          -10
 Val Ile Leu Thr Arg Ile Arg Ser Tyr Leu Gln Asp Pro Ile Trp Arg
 Gly Pro Pro Pro Thr Asn Gly Val Met His Val Asp Glu Cys Val Glu
         15
                             20
 Phe His Arg Leu Trp Ser Ala Met Gln Phe Val Tyr Cys Ile Pro Val
                         35
 Gly Thr Asn Glu Phe Thr Ala Glu Gln Cys Phe Gly Asp Gly Leu Asn
 45 .
                    50
                                         55
 Trp Ala Gly Ser Pro Xaa Leu Ser Cys Xaa Ala Ser Ser Val Ala Leu
                65
 Thr Cys Ser Thr Ser Val Thr Thr Cys
 <210> 1575
 <211> 101
 <212> PRT
 <213> Homo sapiens
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 <221> SIGNAL
 <222> -71..-1
 <400> 1575
Met Ala Leu Val Pro Cys Gln Val Leu Arg Met Ala Ile Leu Leu Ser
    -70
                        -65
Tyr Cys Ser Ile Leu Cys Asn Tyr Lys Ala Ile Glu Met Pro Ser His
-55
                    -50
                                        -45
Gln Thr Tyr Gly Gly Ser Trp Lys Phe Leu Thr Phe Ile Asp Leu Val
                -35
                                    -30
Ile Gln Ala Val Phe Phe Gly Ile Cys Val Leu Xaa Asp Leu Ser Ser
            -20
                                -15
Leu Leu Thr Arg Gly Ser Gly Asn Gln Glu Gln Glu Arg Gln Leu Lys
        -5
                            1
Lys Leu Ile Ser Leu Arg Asp Trp Met Leu Ala Val Leu Ala Phe Leu
                                        20
Leu Gly Phe Leu Leu
<210> 1576
<211> 79
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -69..-1
<400> 1576
Met Ala Thr His His Leu Gly Leu Pro Ala Ser Gln Pro Leu Pro Gly
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~60

Ile Leu Ser Arg Ala Pro Ser Leu Pro Pro Arg Ser Pro Ala Thr Arg

```
-45
  Ser Arg Val Ser Ser Pro Trp Gly Glu Ser Ser Ser Leu Leu Phe
                              -30
  Pro Asp Cys His Ile Ser Phe Pro Ala Leu Thr Gly Ser Gln Leu Leu
                          -15
                                            -10
  Gly Asp Thr Ile Pro Arg Pro His Leu Pro Pro Thr Ala Ala Cys
                      1
  <210> 1577
  <211> 108
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -35..-1
  <400> 1577
  Met Thr Pro Ser Arg Leu Pro Trp Leu Leu Ser Trp Val Ser Ala Thr
                     -30
                                       -25
 Ala Trp Arg Ala Ala Arg Ser Pro Leu Leu Cys His Ser Leu Arg Lys
                 -15
                                     -10
 Thr Ser Ser Ser Gln Gly Gly Lys Ser Glu Leu Val Lys Gln Ser Leu
 Lys Lys Pro Lys Leu Pro Glu Gly Arg Phe Asp Ala Pro Glu Asp Ser
 His Leu Glu Lys Glu Pro Leu Glu Lys Phe Pro Asp Asp Val Xaa Pro
                     35
                                         40
 Val Thr Lys Glu Lys Gly Gly Pro Arg Gly Pro Glu Pro Thr Arg Tyr
                 50
                                     55
 Gly Asp Trp Glu Arg Lys Gly Arg Cys Ile Asp Phe
 <210> 1578
 <211> 81
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -51..-1
 <400> 1578
Met Glu Lys Leu Arg Arg Val Leu Ser Gly Gln Asp Asp Glu Glu Gln
                        -45
Gly Leu Thr Ala Gln Val Leu Asp Ala Ser Ser Leu Ser Phe Asn Thr
                    -30
                                        -25
Arg Leu Lys Trp Phe Ala Ile Cys Phe Val Cys Gly Val Phe Phe Ser
                -15
                                    -10
Ile Leu Gly Thr Gly Leu Leu Trp Leu Pro Gly Gly Ile Lys Leu Phe
Ala Val Phe Tyr Thr Leu Gly Asn Leu Ala Ala Leu Xaa Val His Ala
Xaa
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<210> 1579
<211> 108
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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663 <222> -93..-1 <400> 1579 Met Cys Glu Asn Gln Glu Glu Pro Ala Gly Ser Val Cys Cys His Arg -90 -85 Val Ser Ala Cys Arg Gly Gly Thr Pro Gly Gly Gly Arg Gly Gln Ser -70 His Cys Arg Gly Pro Asp Trp Glu Asn Asn Asp Met Ala Gly Ala Ser -55 Leu Gly Ala Arg Phe Tyr Arg Gln Ile Lys Arg His Pro Gly Ile Ile -40 -35 Pro Met Ile Gly Leu Ile Cys Leu Gly Met Gly Ser Ala Ala Leu Tyr -25 -20 Leu Leu Arg Leu Ala Leu Arg Ser Pro Asp Val Trp Leu Gly Gln Lys -10 -5 Glu Gln Pro Gly Ala Leu Glu Pro Pro Glu Pro Gln 10 <210> 1580 <211> 134 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1

<400> 1580 Met Ala Ala Ala Gly Leu Ala Leu Leu Xaa Arg Arg Val Ser Ser Ala - 5 Leu Lys Ser Ser Arg Ser Leu Ile Thr Pro Gln Val Pro Ala Cys Thr 10 Gly Phe Phe Leu Ser Leu Leu Pro Lys Ser Thr Pro Asn Val Thr Ser Phe His Gln Tyr Arg Leu Leu His Thr Thr Leu Ser Arg Lys Gly Leu Glu Glu Phe Phe Asp Asp Pro Lys Asn Trp Gly Gln Glu Lys Val Lys 55 Ser Gly Ala Ala Trp Thr Cys Gln Gln Leu Arg Asn Lys Ser Asn Glu 70 Asp Leu His Lys Leu Trp Tyr Val Leu Leu Lys Glu Arg Asn Met Leu 90 Leu Thr Leu Glu Gln Glu Ala Lys Arg Gln Arg Leu Pro Met Pro Ser 105 Pro Glu Arg Leu Asp Arg

<210> 1581 <211>.64 <212> PRT <213> Homo sapiens

115

<400> 1581 Met Asn Glu Ser Lys Pro Gly Asp Ser Gln Asn Leu Ala Cys Val Phe Cys Arg Lys His Asp Asp Cys Pro Asn Lys Tyr Gly Glu Lys Lys Thr

Lys Glu Lys Trp Asn Leu Thr Val His Tyr Tyr Cys Leu Leu Met Ser

Ser Gly Ile Trp Gln Arg Gly Lys Glu Glu Glu Gly Val Met Val Phe 50

<210> 1582 <211> 79

664 <212> PRT <213> Homo sapiens <400> 1582 Met Ala Val Ala Arg Ala Gly Val Leu Gly Val Gln Trp Leu Gln Arg Ala Ser Arg Asn Val Met Pro Leu Gly Ala Arg Thr Ala Ser His Met Thr Lys Asp Met Phe Pro Gly Pro Tyr Pro Arg Thr Pro Glu Glu Arg Ala Ala Ala Lys Lys Tyr Asn Met Arg Val Glu Asp Tyr Glu Pro Tyr Pro Asp Asp Gly Met Gly Tyr Gly Asp Leu Phe Leu Xaa Val 70 <210> 1583 <211> 66 <212> PRT <213> Homo sapiens <400> 1583 Met Glu Val Asp Ala Pro Gly Val Asp Gly Arg Asp Gly Leu Arg Glu, 10 Arg Arg Gly Phe Ser Glu Gly Gly Arg Gln Asn Phe Asp Val Arg Pro Gln Ser Gly Ala Asn Gly Leu Pro Lys His Ser Tyr Trp Leu Asp Leu Trp Leu Phe Ile Leu Phe Asp Val Val Val Phe Leu Phe Val Tyr Phe Leu Pro <210> 1584 <211> 45 <212> PRT <213> Homo sapiens <400> 1584 Met Tyr Val Tyr Val Cys Val Trp Val Cys Val Tyr Thr Val Glu Ser 10 Lys Leu Glu Asn Ser Ser Ile Tyr Pro Pro Pro Ser Pro Val Glu Xaa . 20 25 Lys Lys Ile Phe Thr Phe Val Thr Phe Leu Phe Pro Pro 35 <210> 1585 <211> 25 <212> PRT <213> Homo sapiens <400> 1585 Met Gly Pro Gly Gly Ala Leu His Gly Gly Met Lys Thr Leu Leu Pro Trp Thr Ala Arg Ala Ser Arg Ser Pro <210> 1586 <211> 98 <212> PRT <213> Homo sapiens <400> 1586 Met Tyr Gly Lys Gly Lys Ser Asn Ser Ser Ala Val Pro Ser Asp Ser

Gln Ala Arg Glu Lys Leu Ala Leu Tyr Val Tyr Glu Tyr Leu Leu His Val Gly Ala Gln Lys Ser Ala Gln Thr Phe Leu Ser Glu Ile Arg Trp

```
665
  Glu Lys Asn Ile Thr Leu Gly Glu Pro Pro Gly Phe Leu His Ser Trp
  Trp Cys Val Phe Trp Asp Leu Tyr Cys Ala Ala Pro Glu Arg Arg Glu
                                          75
  Thr Cys Glu His Ser Ser Glu Ala Lys Ala Phe His Asp Tyr Val Xaa
                  85 .
  Asn Ile
  <210> 1587
  <211> 50
  <212> PRT
 <213> Homo sapiens
 <400> 1587
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 Arg Thr Leu Lys Arg Asn Gly Ile Ser Pro Pro Asn Gln Glu Gly Leu
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                                  25
 Ala Leu Leu Gly Glu Leu Thr Thr His Lys Gln Met Arg Thr Lys
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 Thr Glu
     50
 <210> 1588
 <211> 32
 <212> PRT
 <213> Homo sapiens
 <400> 1588
 Met Asn Arg Thr Ala Met Arg Ala Ser Gln Lys Asp Phe Glu Asn Ser
                                     10
 Xaa Asn Gln Val Lys Leu Leu Lys Lys Asp Pro Gly Asn Glu Xaa Ser
 <210> 1589
 <211> 58
 <212> PRT
 <213> Homo sapiens
<400> 1589
Met Ala Ser Ser Gly Ala Gly Asp Pro Leu Asp Ser Lys Arg Gly Glu
Ala Pro Phe Ala Gln Arg Ile Asp Pro Thr Arg Glu Lys Leu Thr Pro
            20
Glu Gln Leu His Ser Met Arg Gln Ala Glu Leu Pro Ser Gly Arg Arg
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Ser Tyr His Gly Gly Glu Pro Gly Thr Ser
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<210> 1590
<211> 98
<212> PRT
<213> Homo sapiens
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Met Ser Ser Asp Asp Lys Ser Lys Ser Asn Asp Pro Lys Thr Glu Pro
Lys Asn Cys Asp Pro Lys Cys Glu Gln Lys Cys Glu Ser Lys Cys Gln
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Pro Ser Cys Leu Lys Lys Leu Leu Gln Arg Cys Phe Glu Lys Cys Pro
Trp Glu Lys Cys Pro Ala Pro Pro Lys Cys Leu Pro Cys Pro Ser Gln
Ser Pro Ser Ser Cys Pro Pro Gln Pro Cys Thr Lys Pro Cys Pro Pro
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Lys Cys Pro Ser Ser Cys Pro His Ala Cys Pro Xaa Pro Cys Pro Pro

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Pro Glu
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<210> 1593 <211> 119 <212> PRT <213> Homo sapiens <400> 1593 Met Glu Ala Ser Ala

 Met
 Glu
 Ala
 Ser
 Ala
 Leu
 Thr
 Ser
 Ser
 Ala
 Val
 Thr
 Ser
 Val
 Val
 Val
 Ala
 Ser
 Gly
 Ser
 Ala
 Val
 Val
 Leu
 Ala
 Arg

 Val
 Val
 Arg
 Val
 Ala
 Ser
 Gly
 Ser
 Ala
 Val
 Val
 Leu
 Ala
 Arg

 Ile
 Ala
 Thr
 Val
 Ile
 Gly
 Gly
 Val
 Val
 Ala
 Val
 Pro
 Met
 Val
 Leu

 Ser
 Ala
 Met
 Gly
 Phe
 Thr
 Ala
 Ala
 Gly
 Ile
 Ala
 Ser
 Ser
 Ile
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 Ala

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 Met
 Met
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115

667 <211> 81 <212> PRT <213> Homo sapiens <400> 1594 Met Tyr Ile Gln Cys Cys Glu Trp Leu Gln Ser Trp Arg Ser Lys Asp Glu Phe Cys Leu Glu Glu Ser Gly Lys Ala Ser Trp Arg Arg Glu Gln Trp His Gly Pro Xaa Xaa Val Arg Ser Phe Gln Phe Ile Pro Phe Lys His Cys Ser His Val Ala Phe Lys His Ser Ile Val Leu Ala Val Thr 55 Gln Ala His Ser Ala Lys Gly Ser Thr Ser Phe Ser Ala Met Arg Thr 65 70 Tyr . <210> 1595 <211> 65 <212> PRT <213> Homo sapiens <400> 1595 Met Val Gly Val Ser Val Cys His His Ile Arg Val Gly Ile Lys Arg 10 Arg Lys Ala Ala Leu Leu Glu Leu Cys Gly Leu Leu Gln Val Arg Val Ala Gly Asn Arg Thr Thr Leu Leu Leu Glu Glu Lys Arg Asn Ser Phe 40 Ser Ala Xaa Thr Arg Lys Ala Val Phe Phe Ser Gly Asp Leu His Phe 55 Ser 65 <210> 1596 <211> 111 <212> PRT <213> Homo sapiens <400> 1596 Met Pro Ser Arg Thr Ala Arg Tyr Ala Arg Tyr Ser Pro Arg Gln Arg 10 Arg Arg Arg Met Leu Ala Asp Arg Ser Val Arg Phe Pro Asn Asp Val Leu Phe Leu Asp His Ile Arg Gln Gly Asp Leu Glu Gln Val Gly Arg Phe Ile Arg Thr Arg Lys Val Ser Leu Ala Thr Ile His Pro Ser Gly Leu Ala Ala Leu His Glu Ala Val Leu Ser Gly Asn Leu Glu Cys Val 75 Lys Leu Leu Val Lys Tyr Gly Ala Asp Ile His Gln Arg Asp Glu Ala 90 Gly Trp Thr Pro Leu His Ile Ala Cys Ser Asp Gly Tyr Leu Thr 105 <210> 1597

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668
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  <211> 113
  <212> PRT
  <213> Homo sapiens
  <400> 1598
 Met Asp Pro Asn Pro Arg Ala Ala Leu Glu Arg Gln Gln Leu Arg Leb
                                      10
 Arg Glu Arg Gln Lys Phe Phe Glu Asp Ile Leu Gln Pro Glu Thr Glu
 Phe Val Phe Pro Leu Ser His Leu His Leu Glu Ser Gln Arg Pro Pro
                              40
 Ile Gly Ser Ile Ser Ser Met Glu Val Asn Val Asp Thr Leu Glu Gln
                          55
 Val Glu Leu Ile Asp Leu Gly Asp Pro Asp Ala Ala Asp Val Phe Leu
                      70
 Pro Cys Glu Asp Pro Pro Pro Thr Pro Gln Ser Ser Gly Val Asp Asn
                  85
                                      90
 His Leu Glu Glu Leu Ser Leu Pro Xaa Ala Tyr Ile Arg Gln Asp His
             100
                                  105
 Ile
 <210> 1599
 <211> 58
 <212> PRT
 <213> Homo sapiens
 <400> 1599
Met Val Val Phe Gly Tyr Glu Ala Gly Thr Lys Pro Arg Asp Ser Gly
                                     10
Val Val Pro Val Gly Thr Glu Glu Ala Pro Lys Asp Thr Lys Tyr Ile
Ser Asn Gly Asp Ile Trp Asn Asn Ser Trp Phe Leu Trp Asn Ile Leu
                             40
Lys Leu Pro Val Gln Thr Leu Leu Gln Gly
    50
<210> 1600
<211> 247
<212> DNA
<213> Homo sapiens
<400> 1600
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tattegttaa tggttaatat aaatttaetg etetaggtta ageetaacat atgtaattge
                                                                       120
tactageeta ttaettttta gteeattggg aateactaaa aaaagtagag getttagett
                                                                       180
catteetegg etgettaaat catattgtaa tgttttaaat tgttatgteg teetgtataa
                                                                       240
ccttagg
                                                                       247
<210> 1601
<211> 225
<212> DNA
<213> Homo sapiens
<400> 1601
aaaattattt tgagacaaaa catgggaaag gagggagttg gccaggagtt tatcatgaag
                                                                       60
catatacagg agtcatcccc tacgttgaca ctggtaagtt gacttcagtc acatgaaaca
                                                                       120
tgtcaccttt ccataaatac tccattccct tttgtgattt tgttctttgc acatgttgtt
                                                                       180
ctatctctgc ctggaatgtg ttctccacct tttgattgtc tgcca
                                                                       225
<210> 1602
<211> 258
<212> DNA
<213> Homo sapiens
<400> 1602
gtgaccacag tctgcagagg ccagagagag caggaaagga aatggaaagg aacctcacct
                                                                       60
teatgettgg ggaaaaggag aaacetgtgt taatgtgtet teecaacate ceactetett
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  <223> n=a, g, c or t
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 caggacaaac acaaagaact ctctgcacag ttcattactc cattaggtgg ttcagatgca
                                                                        120
 attccagccc ttagtcaggt tctttccagt gtcctcaaac acagtaagga gagtgctcta
                                                                        180
 agtgactett tgtgteteae acaatetett gggtteeeag gteaetggtg tagtageeag
                                                                        240
 ctgcatccaa gaagccaggt gagcctgtgc caccaatcac agatactcct taccaaccat
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120

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# INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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09/069,047

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(71) Applicant (for all designated States except US): GENSET [FR/FR]; 24, rue Royale, F-75008 Paris (FR).

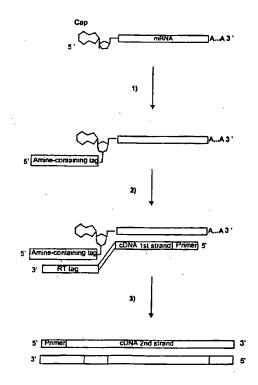
(72) Inventors; and

- (75) Inventors/Applicants (for US only): DUMAS MILNE ED-WARDS, Jean-Baptiste [FR/FR]; 8, rue Grégoire-de-Tours, F-75006 Paris (FR). DUCLERT, Aymeric [FR/FR]; 6 ter, rue Victorine, F-94100 Saint-Maur (FR). GIORDANO, Jean-Yves [FR/FR]; 12, rue Duhesme, F-75018 Paris (FR).
- (74) Agents: MARTIN, Jean-Jacques et al.; Cabinet Regimbeau. 26, avenue Kléber, F-75116 Paris (FR).

(54) Title: 5' ESTS AND ENCODED HUMAN PROTEINS

#### (57) Abstract

The sequences of 5' ESTs derived from mRNAs encoding secreted proteins are disclosed. The 5' ESTs may be to obtain cDNAs and genomic DNAs corresponding to the 5' ESTs. The 5' ESTs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. Upstream regulatory sequences may also be otained using the 5' ESTs. The 5' ESTs may also be used to design expression vectors and secretion vectors.



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Interns (al Application No PCT/IB 99/00712

A. CLASSIFICATION OF SUBJECT MATTER
1PC 6 C12N15/11 C12N15/10 CO7K14/47 C12P21/00 C12Q1/68 C07K16/18 G06F17/30 G06F17/50 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C12N C07K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Category \* Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. BRENNER ET AL.: "Homo sapiens Xq28 Χ 1.2 genomic DNA in the region of the LICAM locus .... EMBL SEQUENCE DATABASE, 9 May 1996 (1996-05-09), XP002121588 HEIDELBERG DE Ac U52112 4-21 the whole document & BRENNER ET AL.: "Genomic organization of two novel genes on human Xq28: compact head to head arrangement of IDH gamma and TRAP delta is conserved in rat and mouse" GENOMICS, vol. 44, no. 1, 1997, pages 8-14, Further documents are listed in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents : T later document published after the international filing date or priority date and not in conflict with the application but "A" document defining the general state of the art which is not considered to be of particular relevance cited to understand the principle or theory underlying the earlier document but published on or after the international "X" document of particular relevance; the claimed invention ocument or particular relevance, the Gailleo Wiverbook
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Interr. .nai Application No PCT/IB 99/00712

	alion) DOCUMENTS CONSIDERED TO BE RELEVANT			to give Ale		
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	substrate, 80 kD protein, heavy chain (PKCSH)"	,				
	SWISSPROT SEQUENCE DATA BASE,	•		. •		
	1 January 1990 (1990-01-01), XP002121589			•-		
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	the whole document					
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1	compound"	•				
	EMBL SEQUENCE DATABASE,	•				
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1	Ac J03075		1			
[	the whole document			•		
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	nucleotide sequence and chromosomal		:			
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	vol. 5, 1989, pages 309-315,					
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	NICOLAEVNA (FR); DUMAS MILNE EDWARDS JEAN)	1	₹			
	7 November 1996 (1996-11-07) cited in the application					
.	page 13, line 24 -page 14, line 14; claim	ľ				
	26					
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-	encoding human somatostatin receptor 2:	1				
	sequence analysis of the 50?-flanking promoter region"		•			
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	vol. 159, no. 2, 4 July 1995 (1995-07-04),					
	page 291-292 XP004042228 ISSN: 0378-1119					
	abstract					
	WATO 5 FT Also House to add an affinite					
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	GENE,					
	vol. 150, 1 January 1994 (1994-01-01),			j		
	pages 243-250, XP002081364 ISSN: 0378-1119			- [		
•	cited in the application			}		
	abstract			1		
	page 245, left-hand column			1		
	-/			1		
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		<del></del>	9/00/12	
C.(Continua Category *	ation) DOCUMENTS CONSIDERED TO BE RELEVANT  Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.	
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Y	LOCKHART D J ET AL: "EXPRESSION MONITORING BY HYBRIDIZATION TO HIGH-DENSITY OLIGONUCLEOTIDE ARRAYS" BID/TECHNOLOGY, vol. 14, no. 13, 1 December 1996 (1996-12-01), pages 1675-1680, XP002022521 ISSN: 0733-222X abstract		8,9	
Υ	WO 98 07830 A (INST GENOMIC RESEARCH ;UNIV PENNSYLVANIA (US); UNIV JOHNS HOPKINS) 26 February 1998 (1998-02-26) page 3, line 4 - line 28 page 31, line 6 -page 35, line 16		7,11-21	
X	MUZNY ET AL.: "Homo sapiens, working draft sequence, 97 unordered pieces" EMBL SEQUENCE DATABASE, 3 February 1998 (1998-02-03), XP002121591 HEIDELBERG DE AC AC004085 the whole document		1,2	
X	ADAMS ET AL.: "EST177394 Jurkat T-cells VI homo sapiens cDNA 5' end similar to protein kinase C substrate 80K-H" EMBL SEQUENCE DATABASE, 18 April 1997 (1997-04-18), XP002121592 HEIDELBERG DE Ac AA306438 the whole document -& ADAMS ET AL.: "Initial assessment of human gene diversity and expression patterns based upon 83 million nucleotides		3	
	of cDNA sequences" NATURE, vol. 377, 1995, pages 3-174, XP002069461			
1	"zr94d07.rl NCI_CGAP_GCB1 Homo sapiens cDNA clone IMAGE:683341 5' EST" EMBL SEQUENCE DATABASE, 5 February 1997 (1997-02-05), XP002121593 HEIDELBERG DE Ac AA215334 the whole document		1,2	
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		PCT/IB 99	9/00/12
	tion) DOCUMENTS CONSIDERED TO BE RELEVANT		
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[	****		·
			*

International application No. PCT/IB 99/00712

# INTERNATIONAL SEARCH REPORT

ROXI	Observations where certain claims	were found unsearchable (Continuation of item 1 of first sheet)
This Int	ternational Search Report has not been esta	blished in respect of certain claims under Article 17(2)(a) for the following reasons:
1. χ	Claims Nos.: because they relate to subject matter not a	required to be searched by this Authority, namely:
	Rule 39.1(v) PCT - Pre Although claim 12 could be Rule 39.1(v) PCT, the sea systematic documentation	pe considered as a mere presentation of information, arch has been carried out as far as possible in our
2.	Claims Nos.: because they relate to parts of the Internat an extent that no meaningful International	ional Application that do not comply with the prescribed requirements to such Search can be carried out, specifically:
	·	
3.	Claims Nos.: because they are dependent claims and are	e not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of inventi	on is lacking (Continuation of Item 2 of first sheet)
This Inte	ernational Searching Authority found multiple	inventions in this international application, as follows:
	<u>&gt;</u>	
	••	
	·	
1.	As all required additional search fees were t	imely paid by the applicant, this international Search Report covers all
	searchable claims.	
2.	As all searchable claims could be searched	without effort justifying an additional fee, this Authority did not invite payment
	of any additional fee.	
	As only some of the required additional sear covers only those claims for which fees were	ch tees were timely paid by the applicant, this International Search Report paid, specifically claims Nos.:
		•
	·	
•		
4. 🙀 ļ	No required additional search fees were time restricted to the invention first mentioned in the	ly paid by the applicant. Consequently, this International Search Report is ne claims; it is covered by claims Nos.:
	Invention 1: 1-21 partiall	y
	·	
•	Donate of	
remark o	n Protest	The additional search fees were accompanied by the applicant's protest.
		No protest accompanied the payment of additional search fees.

# FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 12 could be considered as a mere presentation of information, Rule 39.1(v) PCT, the search has been carried out as far as possible in our systematic documentation.

Continuation of Box 1.1

Rule 39.1(v) PCT - Presentation of information

### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: Invention 1: 1-21 all partially

Nucleic acid comprising a sequence as in Seq.ID.No. 24, complementary sequence and fragments thereof. Polypeptide, Seq.Id.No. 812, encoded by said nucleotide sequence. Vector comprising Seq.Id.No. 24 and host cell comprising the vector. Methods of making cDNA and polypeptide utilising Seq.Id.No. 24. Array of ESTs comprising Seq.Id.No. 24, or a fragment thereof. An antibody binding to an epitop of the polypeptide of Seq.Id.No. 812. A computer readable medium and a computer system storing and/or utilising the sequence of Seq.Id.No. 24 or 812.

2. Claims: Invention 2-811: 1-21 all partially

Idem as subject 1 but limited to each of the DNA sequences as in Seq.Id.No. 25-811 and 1600-1622, and corresponding polypeptides when applicible, where invention 2 is limited to Seq.Id.No. 25 and 813, invention 3 is limited to Seq.Id.No. 26 and 814, ....., invention 788 is limited to Seq.Id.No. 811 and 1599, invention 789 is limited to Seq.Id.No. 1600, invention 790 is limited to Seq.Id.No. 1601, ...., invention 811 is limited to Seq.Id.No. 1622.

Information on patent family members

PCT/IB 99/00712

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WO 9807830	A	26-02-1998	NONE	